

Endometrial stromal sarcoma of the uterus: A study of 8 cases

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Objective : The purpose of this study was to investigate the clinicopathologic findings, treatment, and outcome of patients with endometrial stromal sarcoma (ESS) of the uterus.

Methods : This study retrospectively reviewed 8 patients with histologically proven stage I low-grade ESS of the uterus, at the Department of Obstetrics and Gynecology of Korea University Kuro Hospital, between May 1994 and July 2005, for clinical profiles and survival. The median follow-up was 79 months and ranged from 7 months to 131 months.

Results : The median age at the time of diagnosis was 43 years (range: 29-49 years). The common presenting symptoms were vaginal bleeding, lower abdominal pain and vaginal discharge. Four patients were treated with surgery followed by post-operative adjuvant chemotherapy, and four patients were treated with surgery alone. Recurrence was in one patient, and the site was the lung. The overall five-year survival rate of stage I low-grade ESS was 100%. Bilateral salpingo-oophorectomy and adjuvant chemotherapy did not significantly affect the survival of patients ($p > 0.05$).

Conclusion : The patients with stage I low-grade ESS have a very excellent prognosis. The role of bilateral salpingo-oophorectomy and adjuvant chemotherapy have not yet been clearly defined and further studies, including prospective studies with larger numbers of patients, are needed.

Key Words : Endometrial stromal sarcoma, Low-grade sarcoma, Uterine sarcoma

INTRODUCTION

Endometrial stromal sarcoma (ESS) is a rare neoplasm, which is composed purely of cells resembling normal endometrial stroma. They are classified into a low-grade (LGESS) and a high-grade (HGESS) variety on the basis of mitotic activity. LGESS is distinguished from HGESS microscopically by a mitotic rate of less than 10 mitoses per 10 high-power fields (HPF), as well as clinically by a more protracted course. Recurrences typically occur late, and local recurrence is more common than distant metastases. HGESS is a highly malignant neoplasm. Histologically, it exhibits greater than 10 mitoses per 10 HPF and often completely lacks recognizable stromal differentiation. This tumor has a

much more aggressive clinical course and poorer prognosis than LGESS.

The main symptom of ESS is abnormal vaginal bleeding, while physical examination sometimes shows uterine enlargement and a protrusion of the tumor through the cervical os.¹

Optimum initial therapy for patients with LGESS consists of surgical excision of all grossly detectable tumors. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the standard treatment for women suffering from HGESS, whereas the role of bilateral salpingo-oophorectomy for LGESS is under debate.^{2,3} The roles of radiotherapy and chemotherapy in the adjuvant treatment of ESS on survival are also controversial. The efficacy of chemotherapy in ESS is not clearly proven. The current role of chemotherapy in the treatment of ESS includes the use of various agents in patients with advanced or recurrent HGESS.^{4,5} Recently, reports suggested that pelvic radiation

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is unlikely to confer any survival benefit, but is likely to improve local control only.^{6,7}

Tumor stage, myometrial invasion, mitotic count, tumor size, involvement of surgical margins by the tumor, histologic grade and menopausal status have been reported to have prognostic significance in various studies.⁸⁻¹⁰ However, these findings are still controversial.

The purpose of this study was to investigate the clinicopathologic findings, treatment, and outcome of patients with stage I LGEES of the uterus.

MATERIALS AND METHODS

We reviewed the hospital records, including surgical notes and pathologic reports, of 8 patients with stage I LGEES treated at the Department of Obstetrics and Gynecology of Korea University Kuro Hospital, between May 1994 and July 2005. Clinical data were retrospectively reviewed with regard to age at initial diagnosis, parity, gravidity, pre- or postmenopausal status, presenting symptoms, pathological findings, stage of disease, treatment modality (primary and adjuvant), site of recurrence and results of follow-up. The median follow-up was 79 months and ranged from 7 months to 131 months.

Patients were retrospectively staged according to a modification of the International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer, as

suggested by Berchuck, et al.¹¹ ESS was separated into low-grade and high-grade lesions according to the criteria proposed by Norris and Taylor.¹² The distinction between low-grade and high-grade sarcomas was made solely on the basis of mitotic count. The tumor was considered to be low-grade when there were less than 10 mitotic figures per 10 HPF.

The duration of survival was the primary endpoint. This was determined as the time from the date of diagnosis to the date of death or last follow-up. The cut-off for the survival study was July 31, 2005. The survival curves were calculated by the Kaplan-Meier method. The log-rank test was used to compare survival curves.

RESULTS

Patient characteristics are presented in Table 1. The median age at the time of diagnosis was 43 years (range: 29-49 years). All patients were premenopausal. One patient (12.5%) was nulliparous and 7 (87.5%) had at least one child at the time of diagnosis. The median parity was 2 (range: 0-4). The median gravidity was 4 (range: 1-9). None of the patients had a personal or familial history of ESS. All the patients, except one, were symptomatic. Four of seven patients in whom clinical data were known presented with vaginal bleeding, one presented with lower abdominal pain, one presented with vaginal discharge, and another had an enlarged

Table 1. Patient characteristics of stage I low-grade endometrial stromal sarcoma

Case	Age	Parity	Symptoms	Treatment	Chemotherapy	Recurrence	Follow up (months)
1	44	2-1-3-2	B	TAH & BSO	None	None	NED (84)
2	49	4-0-2-4	B	TAH	CYVADIC	None	NED (131)
3	47	0-0-1-0	B	TAH & BSO	CYVADIC	None	NED (118)
4	42	2-0-7-2	P	TAH	None	None	NED (80)
5	41	2-0-0-2	B	TAH	None	None	NED (47)
6	37	2-0-0-2	M	TAH & BSO&N	TAX & IFOS	None	NED (7)
7	29	2-0-1-2	D	TAH	None	Lung meta	DOD (99)
8	49	2-0-3-2	NO	TAH & BSO	TAX & IFOS	None	NED (78)

B; vaginal bleeding, P; lower abdominal pain, M; myoma uteri, D; vaginal discharge, N; lymphadenectomy, CYVADIC; cyclophosphamide, vincristine, doxorubicin and dacarbazine, TAX & IFOS; taxol and ifosfamide, meta; metastasis, NED; no evidence of disease, DOD; death on disease

uterus due to leiomyomas. Dilatation and curettage did not establish the diagnosis in any of the 4 patients in whom it had been performed prior to explorative laparotomy. In 4 patients, dilatation and curettage had not been performed prior to explorative laparotomy.

Surgery was the initial treatment for all patients. Of the 8 patients who had surgery, 4 had a total abdominal hysterectomy only, and 4 had a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Additionally, pelvic lymph node dissections were performed in 1 patient at the time of the hysterectomy, and the patient had no nodal metastasis.

Of the 8 patients, 4 underwent no postoperative treatment and 4 received combination chemotherapy. Of the 4 patients with postoperative chemotherapy, 2 received cyclophosphamide, vincristine, doxorubicin and dacarbazine (CYVADIC), and 2 received taxol and ifosfamide. Recurrence was in one patient, and the site was the lung. All, except one patient, were still alive with no evidence of disease.

The overall 5-year survival rate of stage I LGEES was 100%. Patients with bilateral salpingo-oophorectomy had no significant difference in their survival than did those with bilateral ovarian conservation ($p=0.4795$). Patients treated with adjuvant chemotherapy had no significant difference in their survival than did those treated with surgery only ($p=0.1573$).

DISCUSSION

ESS is an uncommon group of pure homologous uterine sarcomas. Endometrial stromal sarcoma accounts for 7-15% of all uterine sarcomas. In our series, the frequency of ESS in uterine sarcomas was 38.1%, which was more frequent than in other series. Because of the rarity of this tumor, preoperative diagnostic procedures, standard therapy and prognostic factors in patients with ESS are still controversial.

The mean age of ESS patients ranges from 41 to 48 years.¹³⁻¹⁵ LGEES usually occurs in women younger than 50 years of age, and patients with high-grade ESS tend to be

older than 50 years of age.^{2,13} However, women younger than 20 years of age, affected by low-grade or high-grade ESS, have been reported in the literature.^{2,9} In the present study, the median age was 43 years, which is similar to other reports. The most common presenting symptom in our patients was vaginal bleeding and lower abdominal pain, followed by vaginal discharge. Dilatation and curettage was the method which could be used to diagnose ESS before surgery, but none of the patients was diagnosed as having a malignancy by dilatation and curettage in our series.

Surgery has always been described as the most effective treatment for uterine sarcoma.^{8,10,16-18} Extrafascial hysterectomy with bilateral salpingo-oophorectomy is recommended for HGEES, because it is characterized by high levels of estrogen and progesterone receptors and often responds to hormonal therapy; whereas, the role of bilateral salpingo-oophorectomy for LGEES is under debate.^{2,3} Schwartz et al.,³ reported that patients with LGEES and retained ovaries had a recurrence rate of 100% (6/6), but the recurrence rate was 43% for patients who had oophorectomies at the time of the initial surgery. However, Gadduci et al.,² reported that among stage I LGEES patients younger than 50 years of age who underwent a total abdominal hysterectomy, recurrent disease developed in 33.3% of the 6 patients who had bilateral salpingo-oophorectomy and in 16.7% of the 6 patients who were left with residual ovarian tissue. In our series, bilateral ovarian conservation did not significantly influence the prognosis of the disease.

There are very few studies of lymph node involvement in ESS. Riopel et al.¹⁹ reported that lymph node metastasis in five (33%) of 15 patients with low-grade ESS underwent lymph node dissection during surgical treatment, and suggested that the incidence of lymph node involvement in low-grade ESS is higher than expected. In contrast, a review of eight autopsies of patients who died with ESS before 1994 documented lymph node metastasis in only one (12%).²⁰ Another report showed that none of the seven patients with ESS had lymph node involvement.²¹ It is difficult to analyze the incidence of lymph node metastasis in patients with ESS, because the disease is a rarity, and the true value of

a lymphadenectomy in ESS is unknown. However, the high recurrence rate may be due, in part, to occult lymph node metastases, and patients with advanced ESS should undergo a lymphadenectomy.²² In our series, since only one patient underwent a lymphadenectomy, the effect of this treatment could not be analyzed statistically.

The efficacy of adjuvant therapy in patients with ESS is still not proven. One study reported no difference in recurrence rates in patients receiving surgery with adjuvant therapy versus surgery alone.⁶ In several studies, it was also suggested, that chemotherapy has not been proven to be effective in recurrent disease.^{4,5} Postoperative radiotherapy has been shown to reduce the central tumor, but not distal recurrences and it has not improved overall survival.^{5,6} Weitmann et al.,²³ reported that the overall local control rate of adjuvant radiation therapy was 93.8% after 5 years, and concluded that surgery and adjuvant therapy were the most effective treatments for patients with ESS, due to the excellent local control in all stages. Reeds⁷ also suggested that pelvic radiation is unlikely to confer any survival benefit, but is likely to improve local control only. Our results revealed that adjuvant chemotherapy had no influence on the outcome of the disease. Since none of our patients was treated with radiotherapy and hormonal therapy, the possible role of this therapy could not be determined.

In most cases, the overall survival rates for patients suffering from uterine sarcomas are poor. However, a higher survival probability for patients with LGESS compared to other uterine sarcomas is often reported.^{24,25} In the present study, the 5-year overall survival was 100%. This finding is superior to the survival rates reported by Haberal and colleagues,⁹ who observed an overall survival rate of 92%. Bodner et al.,⁸ reported that early tumor stage, low myometrial invasion, and low mitotic count, were associated with a lengthened overall survival in patients with ESS. In another study, free resection margins at primary surgery, malignancy grade, tumor diameter, and menopausal status were important prognostic factors either in univariate or multivariate analyses.¹⁰ However, Haberal et al.,⁹ suggested that tumor grading was the only prognostic factor in ESS

in a multivariate analysis.

Clinical characteristics of Stage I LGESS include a slow growth and indolent disease course with a tendency for late recurrence. In one large series, the intervals before recurrence varied from 3 months to 23 years, with a median interval of 3 years.²⁶ Styron et al.,²⁷ described the case of a patient with LGESS, who experienced multiple recurrences during 29 years of follow-up. About 32-60% of patients with ESS experience a recurrence after the initial treatment.^{2,8,9} Haberal et al.,⁹ reported that eight of 25 patients (32%) had a recurrence: three patients had a recurrence limited to the pelvis, three patients had pulmonary metastases, one had a recurrence in the abdomen, and one in the brain. Relapses occurred mainly in the pelvis, peritoneal cavity, and vagina; and less frequently in the lung, bowel, bones, and brain.^{2,8,9} In our study, we found that one of 8 patients (12.5%) had a recurrence, which occurred in the lung after 7 years.

In conclusion, we found that patients with stage I LGESS had a very excellent prognosis. Additional studies, including prospective studies with larger numbers of patients, are necessary to define the exact role of lymphadenectomy and to determine the prognostic factors associated with LGESS.

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자궁내막기질육종 8예에 대한 임상적 고찰

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목적 : 자궁내막기질육종은 드문 악성종양으로 수술 전 진단과 치료가 아직 정립되지 않아, 이 연구로 자궁내막기질육종의 임상병리학적 소견 및 대상 환자들의 치료 및 예후를 알아보고자 하였다.

연구 방법 : 본 연구는 1994년 5월부터 2005년 7월까지 고려대학교 의과대학부속 구로병원에서 진단되었던 임상병기 1기인 저등급 자궁내막기질육종 8예에 대해 후향적으로 조사했다. 추적관찰기간 분포는 7개월에서 131개월 사이였고 중앙추적기간은 79개월이었다.

결과 : 자궁내막기질육종 환자의 연령분포는 29세에서 49세 사이였고, 중앙연령은 43세였으며 주된 증상으로는 질출혈, 하복부동통 및 질분비물 등이었다. 8명 환자 중 4명의 환자는 수술적 치료만 시행되었고, 다른 4명의 환자는 수술적 치료 후 항암화학요법의 보조적 치료를 시행 받았다. 재발한 경우는 1예로 폐에 전이되었다. 5년 생존율은 100% 이었다. 양측난소난관절제술과 보조적 항암화학요법은 환자의 생존율에 유의하게 영향이 없었다($p > 0.05$).

결론 : 임상병기 1기인 저등급 자궁내막기질육종은 예후가 매우 좋은 종양이다. 양측난소난관절제술과 보조적 항암화학요법의 역할은 아직 분명하지 않으며 향후 보다 많은 수에서 전향적 연구가 필요하리라 생각된다.

중심단어 : 자궁내막기질육종, 저등급 육종, 자궁육종