Gynecologic Oncology 132 (2014) 654–660

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Ovary and uterus-sparing procedures for low-grade endometrial stromal sarcoma: A retrospective study of 153 cases☆,☆☆

Huimin Bai [a], Jiaxin Yang [a], Dongyan Cao [a], Huifang Huang [a], Yang Xiang [a], Ming Wu [a], Quancai Cui [b], Jie Chen [b], Jinghe Lang [a], Keng Shen [a,*]

[a] Department of Obstetrics and Gynecology, Peking Union Medical College (PUMC) Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, China
[b] Department of Pathology, Peking Union Medical College (PUMC) Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, China

HIGHLIGHTS

- Hysterectomy with bilateral salpingo-oophorectomy and complete resection of the macroscopic lesion should be treated as the mainstay treatments for LG-ESS.
- Ovary-sparing procedures could be considered for young women without cervical involvement; however, long-term follow-up should be mandatory.
- Myomectomy should only be conserved for young patients with a strong desire for future fertility, with fully informed consent.

ARTICLE INFO

Article history:
Received 10 October 2013
Accepted 23 December 2013
Available online 9 January 2014

Keywords:
Endometrial stromal sarcoma
ESS
Low grade
Prognosis
Recurrence
Treatment

ABSTRACT

Objective. To discuss the optimal treatment options for low grade endometrial stromal sarcoma (LG-ESS).

Methods. Medical records of consecutive patients with LG-ESS in our institute were collected. The pertinent data, including clinicopathological characteristics, treatment and prognostic information were evaluated.

Results. A total of 153 cases of LG-ESS were included. The 5-year relapse free survival (RFS), overall survival (OS) and survival after relapse (SAR) rates were 66.1%, 95.8% and 82.9%, respectively. Ovary-sparing procedures, positive resection-margins, and myomectomy were the independent adverse factors for relapse ($P < 0.0001$, $= 0.0041$, and $= 0.0075$, respectively). Post-menopause, cervical involvement, and positive lymphovascular space involvement were significantly associated with survival ($P < 0.0001$, $= 0.0020$, and $= 0.0163$, respectively). Distance recurrence and macroscopically residual tumors negatively affected SAR ($P = 0.0137$ and $= 0.0004$, respectively). No benefit was found for lymphadenectomy in terms of both RFS and OS ($P = 0.1187$ and $= 0.5138$, respectively). Initial ovary-sparing procedures and myomectomy had no impact on OS ($P = 0.0810$ and $= 0.8845$, respectively). Adjuvant treatment had a slightly beneficial effect both on OS and SAR.

Conclusion. Hysterectomy with bilateral salpingo-oophorectomy and complete resection of the macroscopic lesion should be treated as the initial and salvage mainstay treatments for LG-ESS patients. Ovary-sparing procedures could be considered for young women without cervical involvement; however, long-term follow-up should be mandatory. Myomectomy should only be conserved for young patients with a strong desire for future fertility, with fully informed consent; hysterectomy was recommended after the completion of pregnancy and delivery. However, the roles of lymphadenectomy and adjuvant treatment deserve further investigation.

Introduction

Endometrial stromal sarcoma (ESS) is a rare tumor that represents approximately 7–15% of all uterine sarcomas but only 0.2% of all uterine malignancies [1]. Based on the mitotic rate, ESS is histologically divided into two groups: high-grade (HG) and low-grade (LG) [2]. HG-ESS is currently defined as an undifferentiated endometrial sarcoma (UES), characterized by more than 10 mitoses per 10 high-power fields (HPFs). Additionally, this sarcoma is more aggressive and has a poorer prognosis. In contrast, LG-ESS has fewer than 10 mitoses per 10 HPFs, and the cell nuclei are not atypical or pleomorphic [2]. LG-ESS is relatively more common and tends to occur before menopause. LG-ESS usually exhibits a more indolent clinical course, but has high relapse potential [3]. These two distinct entities should be treated differently.

For LG-ESS, hysterectomy is the cornerstone of treatment. However, the role of a bilateral salpingo-oophorectomy (BSO), as well as lymphadenectomy for complete surgical staging, is debated. Adjuvant treatment, including hormonal treatment, chemotherapy and radiotherapy, has also not been established. The absence of consensus on the optimal

☆ Source of the study: Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (PUMCH).
☆☆ Grant support: National Science and Technology Infrastructure Program "The National Key Technologies R&D Program of China" (Grant 2008BAI57B02).
* Corresponding author. Fax: +86 10 65212507.
E-mail addresses: shenkeng@vip.sina.com, skpumch@126.com (K. Shen).

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.12.032

management of this disease is due to its rarity and the heterogeneity of previously published series, the majority of which included HG tumors and other histologic subtypes of uterine sarcoma [4]. In the present study, we focused exclusively on LG-ESS and compiled 153 cases that were treated at our center, representing one of the largest series that has been published. Our experience in managing this uncommon condition and a review of related literature will also be discussed.

Patients and methods

The medical records of women with LG-ESS who were diagnosed and treated at Peking Union Medical College Hospital (PUMCH) were collected. All consecutive patients who underwent surgery and had complete pathology and operation reports were included in the study, whereas patients who were lost to follow-up immediately after surgery were excluded. Clinical data, including clinicopathological variables, treatment, and follow-up information, were then evaluated.

In our series, hysterectomy was the major surgical procedure. Ovary-sparing procedures and lymphadenectomies were generally performed, depending on the patient's age, their informed consent, the extent of disease, and the institutional practices at the time. Two independent pathologists with extensive backgrounds in gynecological pathology reviewed all pathological slides according to the 2003 WHO Classification and were blinded to the patients' outcomes. The marginal status was interpreted as positive when sarcoma was found at the margins of myomectomy specimens or in the parametria, cervix or vagina of hysterectomy specimens. Macroscopically residual tumor was defined as residual tumor greater than 2 cm in greatest diameter. Staging of the disease was retrospectively performed according to the 2009 FIGO staging system. In cases of incomplete surgical staging, the stage was assessed based on available pathologic findings, with unevaluated areas considered as negative for metastatic lesions, and on the operative records [5].

Adjuvant treatment was performed without well-defined protocols. The decision to administer hormonal treatment, chemotherapy, or radiotherapy was based on the extent of disease, medical comorbidities, institutional practices, or the doctor's preference. For hormonal treatment, megestrol acetate (160 mg/d) or an anti-aromatase inhibitor (250 mg/d) was commonly administered for 6 months. Alternatively, 3–4 monthly injections of GnRHa were used. The main adjuvant intravenous chemotherapy regimens consisted of PEI (70 mg/m^2 cisplatin, d1–3; 60 mg/m^2 epirubicin, d1; 1.5 g/m^2 ifosfamide, d1–3; 0.2 g mesna, 0, 4, or 8 h post-ifosfamide application, d1–3, q28 days), PAC (50 mg/m^2 cisplatin; 50 mg/m^2 adriamycin; 500 mg/m^2 cyclophosphamide, iv, q28 days), and VAC (2 mg vincristine; 75 mg/m^2 adriamycin; 1200 mg/m^2 cyclophosphamide, iv, q28 days). In total, 3–6 chemotherapy cycles were administered. The main radiation type was pelvic radiotherapy with or without a vaginal boost. Brachytherapy and whole-abdominal radiotherapy were also applied according to the site and extent of the patients' disease.

After the treatment completion, the women were followed-up monthly in the first half of the year, every 3 months in the second half of the year, and every 6 months thereafter. For women for whom regular follow-up information was not available, an effort was made to contact these patients by telephone or letter to obtain this information.

Relapse was defined by clinical or imaging evidence and was confirmed pathologically. Local relapse was defined as pelvic or vaginal recurrence, and distant relapse was defined as recurrence in extra-pelvic locations. Relapse-free survival (RFS) times were calculated as the period between the date of initial surgery and the date of relapse; women living disease free at the time of their last visit were censored. OS times were calculated in months from the date of initial surgery to the date of patient death from the disease, and survival after relapse (SAR) was defined as the time from relapse to the date of patient died from the disease or of the last follow-up; patients who died from other conditions and survivors at the time of their last visit were censored.

The study protocol was approved by the ethics committee at PUMCH, Beijing, China.

Statistical analysis

All statistical analyses were performed using SAS® Version 9.2 (SAS Institute, Cary, NC). All tests were 2 sided, and $P < 0.05$ was considered statistically significant. The Kaplan–Meier method was used to analyze the relapse and survival rates. A log rank test was used to compare the different survival curves. A Cox proportional hazards model was used to assess all parameters that were found to be significant in univariate analysis.

Results

Demographic characteristics and clinical presentation

From July 1979 to May 2013, 196 consecutive women with ESS were treated at PUMCH. In total, 32 cases were diagnosed as UES and were excluded from this study. A total of 11 patients (6.7%) were lost to follow-up immediately after surgery, 7 of whom preferred to continue treatment at hospitals near their residences due to their economic conditions. For the other 4 patients, relevant data were not available in their records. All of these patients were excluded from the analysis. Therefore, 153 LG-ESS cases were ultimately included. The clinicopathological characteristics and treatment profiles of these patients are reported in Tables 1 and 2. The patients' mean age at initial diagnosis was 41.8 ± 10.7 (range: 15–79) years, and 136 (89.5%) cases involved premenopausal women, including 22 (14.4%) non-nulliparous women. No

Table 1
Clinical profile of the 153 cases with LG-ESS.

Parameter	Number of patient	Percent (%)
Age at diagnosis, y (mean; range)	41.8; 15–79	
Menstruation status		
Premenopause	136	88.9
Postmenopause	17	11.1
Presentation		
Metrorrhagia	74	48.4
Pelvic pain or pelvic pressure	18	11.8
Rapid growth of leiomyoma	10	6.5
None	47	30.7
n.a.[a]	4	2.6
Preoppresumptive diagnosis		
Asymptomatic leiomyoma	109	71.2
Adenomyosis	9	5.9
ESS (LG or HG)	19	12.4
Others	16	10.5
Primary surgery		
Myomectomy	19	12.4
Hysterectomy	134	87.6
BSO[a]	109	71.2
Lymphadenectomy	46	30.1
Adjacent treatment		
HT[a]	55	35.9
CT[a]	27	17.6
RT[a]	33	21.6
Observation	67	43.8
Follow-up (month; range)	74.2 (1–396)	
Relapse		
No	104	68.0
Yes	49	32.0
Current status		
NED[a]	129	84.3
AWD[a]	15	9.8
DOD[a]	9	5.9

[a] n.a.: Data not available; BSO: bilateral salpingo-oophorectomy; HT: Hormonal treatment; CT: Chemotherapy; RT: Radiation treatment; NED: No evidence of disease; AWD: Alive with disease; DOD: Die of disease.