Article Evaluation of treatment strategies and prognostic factors of 135 patients with low-grade endometrial stromal sarcoma

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Abstract

Background: To evaluate the influence of treatment modalities and prognostic factors on the survival of patients with low-grade endometrial stromal sarcoma (LGESS). Methods: One hundred and thirty-five LGESS patients in Fudan University Shanghai Cancer Center from January 2006 to December 2018 were retrospectively reviewed. Results: Two patients received fertility-sparing surgery while 133 patients received hysterectomy. The median follow-up duration was 52 months (3–342 months). One hundred and nine (80.7%) patients received ovariectomy, 73 (54.1%) patients had lymphadenectomy, 83 (61.5%) patients received adjuvant therapy. The 5-year and 10-year disease free survival rates were 72.0% and 61.0%, respectively. The 5-year and 10-year overall survival rates were 88.0% and 79.8%, respectively. Surgery for recurrence was associated with improved overall survival although the complication rate was about 27.6%. Multivariate analysis showed that lymphovascular invasion was associated with disease free survival (hazard ratio, 0.473; 95% confidence interval, 0.235–0.952; p=0.036) and menopausal status was related to overall survival (hazard ratio, 5.561; 95% confidence interval, 1.400–22.084; p=0.015).

Conclusions: There was no effect of lymphadenectomy, ovariectomy, or adjuvant therapy on patients’ recurrence and survival. Hysterectomy may be proposed as the standard treatment for LGESS. Surgery for relapse was an acceptable method to improve overall survival. Lymphovascular invasion was a significant independent factor for disease free survival. Postmenopause was the poor prognostic factor for overall survival.

Background

Endometrial stromal sarcoma (ESS) is a relatively rare tumor that accounts for approximately 0.2% of uterine malignancies, 20% of uterine sarcomas [1]. There are 3 categories of ESS: undifferentiated uterine sarcoma (UUS), low-grade endometrial stromal sarcoma
sarcoma (LGESS), and high-grade endometrial stromal sarcoma (HGESS) according to the 2014 World Health Organization (WHO) Classification of Tumors [2-4].

LGESS is the most common type of ESS, and hysterectomy is regarded as the main treatment [5]. However, the roles of other therapies such as ovarian preservation, lymphadenectomy, and adjuvant therapy, remain controversial. Because of universal expression of estrogen and progesterone receptors [6], bilateral salpingo-oophorectomy (BSO), or hormone therapy, or both together, were postulated. The value of hormone therapy for early-stage ESS remains unproven [7]. LGESS is defined by a low mitotic index, and so is considered to be insensitive to chemotherapy. Radiation was not associated with increased survival for LGESS [8]. The effect of lymphadenectomy was also uncertain. Controversy still surrounded the prognostic values of the factors such as stage, lymph node metastasis, lymphovascular invasion, and menopause. This retrospective study aimed to evaluate different treatment methods and prognostic factors in LGESS patients who were treated in Fudan University Shanghai Cancer Center over a 12-year period.

Methods

The Review Board of Fudan University Shanghai Cancer Center approved the study. All the cases of endometrial stromal sarcoma from January 2006 to December 2018 were reviewed. Data were collected from medical records in our institutional databases. The study included the patients who had been pathologically diagnosed according to 2014 WHO classification and staged based on International Federation of Gynecology and Obstetrics (FIGO) 2009 staging classification. The pathology was conducted by experienced pathologists of our hospital (cases from other hospitals were all taken for consultation).

The surgery generally included total hysterectomy ± BSO ± lymphadenectomy. For the two patients who wanted to preserve the fertility, hysteromyoma was suggested. For
patients with the involvement of other sites, cytoreductive surgeries were performed.

Hormone therapy comprised Megestrol acetate 160 mg/d or Letrozole 2.5 mg/d or Medroxyprogesterone acetate 500 mg/d.

For patients with adjuvant radiotherapy, the radiation treatment included external pelvic irradiation (18 MV X-rays) with one fraction of 1.8–2.0 Gy daily for a total dose of 50 Gy in 5–6 weeks.

Chemotherapy comprised one of the following combinations: cisplatin 50 mg/m² (d1) + cyclophosphamide 500 mg/m² (d1) + doxorubicin 50 mg/m² (d1), or gemcitabine 900 mg/m² (d1, 8) + docetaxel 100 mg/m² (d8), or doxorubicin 60 mg/m² (d1) + ifosfamide 1.5 g/m² (d1-4). Chemotherapy was generally done in 3–6 cycles over a 3-week period.

The relevant factors in the medical records were listed: age, menopausal status, patient’s symptom, laparoscopic myomectomy, tumor size, muscular infiltration, lymphovascular invasion, lymph node metastasis, FIGO stage, lymphadenectomy, ovariectomy, adjuvant therapy, residual disease, and recurrence. The diagnosis for each case was based on surgical pathology. When the recurrence was suspected, the patients would be examined by Computed Tomography (CT), or Magnetic Resonance Imaging (MRI), or Positron Emission Tomography-Computed Tomography (PET-CT), or tumor pathology on the basis of physical examination. The median follow-up duration was 52 months (3–342 months). The overall survival was calculated as the months from the date of surgery to either the date of last follow up or the date of death. The disease free survival was calculated as the months from the date of surgery to either the date of last follow up or the date of the first recurrence.

All statistical analyses were done with Statistic Package for Social Science (SPSS) version 16.0 (Incorporated, Chicago, Illinois, the United States). The disease free survival and
overall survival were analyzed by the Kaplan-Meier method. Log-rank tests were done in the univariate analyses and Cox regression analysis were used for the multivariate analyses. A p-value less than 0.05 was considered statistically significant.

Results

Clinicopathologic factors and treatment strategies of LEGSS patients

Of 153 ESS during the study period, 135 (88.2%) patients were identified as LGESS while 15 (9.8%) HGESS and 3 (2.0%) UUS patients were excluded in the analysis.

Clinicopathological characteristics were presented in Table 1. Median age at diagnosis was 41.2 years (19-65 years). One hundred and eighteen patients (87.4%) were premenopausal. Most (62.2%) patients had no symptoms and the second symptom was abnormal vaginal bleeding in 37 (27.4%) patients. Leiomyoma was the common clinical diagnosis before we got the pathology. So 30 (22.2%) patients had the history of laparoscopic myomectomy and 56 (41.5%) patients received a secondary operation after the first surgery was hysteromyoma or subtotal hysterectomy.

Large tumor size (≥5 cm) was found in 96 (71.1%) cases. Deep muscle infiltration was observed in 103 (76.3%) patients. Positive lymphovascular invasion was in 33 (24.4%) patients. Lymph node metastasis was shown in 9 (6.7%) patients. FIGO staging indicated that 108 patients (80.0%) had stage I, 13 (9.6%) had stage II, 12 (8.9%) had stage III, and 2 (1.5%) had stage IV.

Table 2 summarized the different treatments and outcomes in 135 LGESS patients. Two patients received fertility-sparing surgery and 133 patients received hysterectomy. One hundred and nine (80.7%) patients received ovariectomy and 73 (54.1%) patients had lymphadenectomy. Fifty-two (38.5%) patients had no adjuvant treatment, 38 (28.1%) patients received hormone therapy, 22 (16.3%) patients had radiotherapy and hormone therapy, and 23 (17.0%) patients received chemotherapy and hormone therapy. Ten
(7.4%) patients had residual disease after the operations.

**Survival and recurrence**

The patients were followed up for a median duration of 52 months (3-342 months). The 5-year and 10-year disease free survival rates were 72.0% and 61.0%, respectively (Fig. 1A). The 5-year and 10-year overall survival rates were 88.0% and 79.8%, respectively (Fig. 1B). Thirty-nine (28.9%) patients had disease recurrence, with a median time to recurrence of 24 months (1-321 months). The distribution of recurrences according to the stage of disease was as follows: 29 out of 108 (26.9%) patients were stage I, 5 out of 13 (38.5%) stage II and 5 out of 12 (41.7%) stage III. Pelvis was the main recurrent site in 76.9% (30 of 39) patients. The other recurrent sites included intestine (n=4), omentum (n=1), liver (n=2), and lung (n=2).

The median survival after recurrence was 17 months (1-177 months) and 29 patients received cytoreductive surgery for recurrences. It was associated with improved mean survival of 47.5 months as compared to mean survival of 14.8 months in 10 patients without it. It was also related to improved overall survival (p<0.05, Fig. 2). The main surgical complications for recurrent diseases were as follows: hemorrhage (n=2), infection (n=3), intestinal fistula (n=2), and urinary fistula (n=1). The complication rate was 27.6%.

At the time of last follow up, 17 patients had died of cancer-related diseases.

**Treatment modalities and clinicopathologic factors associated with disease free survival or overall survival**

In univariate analyses for disease free survival, menopausal status was associated with disease free survival (p<0.05). So were deep muscle infiltration (p<0.05) and lymphovascular invasion (p<0.01). However, upon multivariate analyses, only lymphovascular invasion remained as an independent predictor of disease free survival (hazard ratio, 2.062; 95 % confidence interval, 1.040-4.086; p=0.038) (Fig. 3A).
In univariate analyses for overall survival, menopausal status was associated with overall survival \((p<0.01)\). So were FIGO stage \((p<0.05)\), lymphovascular invasion \((p<0.05)\), lymph node metastasis \((p<0.05)\), residual disease \((p<0.05)\), and recurrence \((p<0.01)\). However, upon multivariate analyses, only menopausal status remained as an independent predictor of overall survival (hazard ratio, 3.691; 95% confidence interval, 1.012–13.457; \(p=0.048\)) (Fig. 3B).

When we further assessed different treatment methods and prognostic factors in 108 LGESS patients with stage I, we still found the similar results (data not shown).

Discussion

Endometrial stromal sarcomas were rare uterine malignancies that might manifest through abnormal uterine bleeding (55.2%) and pelvic mass (28.1%) [1]. In our study, the majority (62.2%) of LGESS patients had no symptoms and the second symptom was abnormal vaginal bleeding in 37 (27.4%) patients (Table 1). Because the preoperative diagnosis was ambiguous and the intraoperative frozen pathology had its limitation, almost all the patients were diagnosed postoperatively. Thus, 56 (41.5%) patients received a secondary operation after the first surgery was hysteromyoma or subtotal hysterectomy. Moreover, laparoscopy was often used in the first operation. Choo suggested that intrapelvic dissemination was due to electronic morcellation [9]. A consensus review suggested morcellation should be avoided [10]. However, we found the history of laparoscopic myomectomy was related to neither overall survival nor disease free survival.

The mean age at diagnosis was 41.2 years (19-65 years) and 118 patients (87.4%) were premenopausal. Therefore, it was worth considering fertility-sparing surgery or ovarian preservation. Zhou suggested that ovarian preservation had no significant effect on disease free survival and ovarian preservation was feasible [1]. It was also reported that fertility-sparing surgery may be considered for early-stage LGESS patients [11, 12].
Rather, some study suggested that the removal of the adnexa might be helpful to decrease the risk of recurrence [13]. In our study, 2 patients received fertility-sparing surgery with adjuvant hormone therapy after operation and no recurrences occurred yet. Moreover, our analysis showed that ovarian removal had no significant effect on disease free survival \( (p=0.443) \) and overall survival \( (p=0.854) \).

According to 2009 FIGO guidelines, initial complete staging for endometrial stromal sarcoma would need lymphadenectomy. Previous studies demonstrated that the incidence of lymph node metastasis ranged from 16% to 33% [14, 15]. In our study, 73 patients received lymphadenectomy and only 9 cases had lymph node metastases. Currently, the benefit of lymph node resection in LGESS is controversial. One meta-analysis suggests that lymphadenectomy bore little prognostic or therapeutic benefit in patients with uterine sarcoma [16]. However, another study showed total hysterectomy with BSO followed by pelvic lymphadenectomy was associated with an improved outcome [17]. Our data found that lymphadenectomy had no effect on both disease-free survival \( (p=0.246) \) and overall survival \( (p=0.652) \). So, we did not advocate the integration of lymphadenectomy in LGESS.

The ability of adjuvant treatment in patients with uterine sarcomas was unclear and there was no standard recommendation regarding adjuvant therapy [18]. Schick found that adjuvant radiotherapy was an independent prognostic factor for overall survival [19]. Use of adjuvant chemotherapy and radiotherapy were reported to be associated with better prognosis only for HGESS [8, 20]. Cade’s study did not regard primary adjuvant progestogen as a survival benefit [21]. Our analyses showed that adjuvant therapy was not associated with disease-free survival or overall survival.

The recurrent rate increased with the development of the stage in our paper. The median time to recurrence was 24 months (1-321 months). Twenty-nine (74.4%) out of 39
recurrent LGESS patients received cytoreductive surgery. The surgery for recurrence was associated with improved overall survival although the complication rate was about 27.6%. Yamazaki also found that the post-relapse survival of patients with endometrial stromal sarcoma can be expected to be >10 years when treated by repeated surgical resection [22]. So repeated surgery for recurrent disease should be an acceptable method. The 5-year relapse free survival and overall survival rates were 66.1% and 95.8% [23]. In our study, the 5-year disease free survival and overall survival rates were 72.0% and 88.0%. Khatib found that stage, age, lymphovascular invasion, and lymphadenectomy were independent prognostic factors for disease free survival and so was stage for overall survival [24]. Another paper showed that age, lymphadenectomy, stage I, and adjuvant therapy did not affect disease free survival or overall survival [25]. On multivariate analysis, only lymphovascular invasion was an independent predictor for disease free survival and so was menopausal status for overall survival in our research. So we suggested lymphovascular invasion was a high risk factor for recurrence and uterine tumors after menopause are well worth our attention.

Conclusions

In conclusion, lymphadenectomy, ovariectomy, or adjuvant therapy had no effect on survival in LGESS patients. Hysterectomy may be proposed as the standard treatment. Cytoreductive surgery for relapse could improve overall survival in recurrent cases. Lymphovascular invasion was a significant independent factor for disease free survival. Post-menopause was the poor prognostic factor for overall survival. We also found the similar results in LGESS patients with stage I.

Abbreviations

Endometrial stromal sarcoma (ESS); undifferentiated uterine sarcoma (UUS); low-grade
endometrial stromal sarcoma (LGESS); high-grade endometrial stromal sarcoma (HGESS); World Health Organization (WHO); bilateral salpingo-oophorectomy (BSO); International Federation of Gynaecology and Obstetrics (FIGO); Computed Tomography (CT); Magnetic Resonance Imaging (MRI); Positron Emission Tomography-Computed Tomography (PET-CT); Statistic Package for Social Science (SPSS)

Declarations

Ethics approval and consent to participate

This study was conducted according to the declaration of Helsinki and was approved by the Committee of Fudan University Shanghai Cancer Center.

Consent for publication

Written informed consents were obtained from all individual participants included in the study.

Availability of data and materials

The institutional database involves sensitive patient information, which is available upon request. Anyone who is interested in the information should contact huangyan1168@aliyun.com.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yan Huang participated in the study design, carried out the data collection, performed the statistical analysis, and revised the manuscript. Huaying Wang carried out the data
collection, performed the statistical analysis and drafted the manuscript. Shanhui Liang and Zheng Feng carried out the data collection. Jun Zhu and Lingfang Xia conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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Tables

Table 1 Clinicopathological characteristics of LGESS patients (n=135).

| Characteristics                      | n (%)       |
|--------------------------------------|-------------|
| Age (years)                          | Median (range) |
|                                       | 41.2(1)     |
|                                       | 50          |
|                                       | 112(83)     |
|                                       | ≥50         |
|                                       | 23(17)      |
| Menopausal status                    | Premenopausal |
|                                       | 118(87)     |
|                                       | Postmenopausal |
|                                       | 17(12)      |
| Patient’s symptom                    | No          |
|                                       | 84(62)      |
|                                       | Abnormal vaginal bleeding |
|                                       | 37(27)      |
|                                       | Abdominal pain |
|                                       | 12(8.9)     |
|                                       | Others      |
|                                       | 2(1.5)      |
| Laparoscopic myomectomy              | Yes         |
|                                       | 30(22)      |
|                                       | No          |
|                                       | 105(77)     |
| Tumor size                           | ≤5cm        |
|                                       | 39(28)      |
|                                       | ≥5cm        |
|                                       | 96(71)      |
| Muscular infiltration                | ≤1/2        |
|                                       | 32(23)      |
|                                       | ≥1/2        |
|                                       | 103(76)     |
| Lymphovascular invasion              | Yes         |
|                                       | 33(24)      |
|                                       | No          |
|                                       | 102(75)     |
| Lymph node metastasis                | Yes         |
|                                       | 9(6.7)      |
|                                       | No          |
|                                       | 126(92)     |
| FIGO stage                           | I           |
|                                       | 108(80)     |
|                                       | II          |
|                                       | 13(9.6)     |
|                                       | III         |
|                                       | 12(8.9)     |
|                                       | IV          |
|                                       | 2(1.5)      |

Table 2 Different treatments and outcomes in patients with LG-ESS (n=135).
| Characteristics                  | n (%)          |
|---------------------------------|----------------|
| Hysterectomy                    | Yes 2(1.5%)    |
|                                 | No 133(98.5%)  |
| Lymphadenectomy                 | Yes 73(54.1%)  |
|                                 | No 62(45.9%)   |
| Ovariectomy                     | Yes 109(80%)   |
|                                 | No 26(19.3%)   |
| Adjuvant therapy                | No 52(38.1%)   |
|                                 | Hormonal therapy 38(28.4%) |
|                                 | Radiotherapy and hormonal therapy 22(16.3%) |
|                                 | Chemotherapy and hormonal therapy 23(17.1%) |
| Residual disease                | Yes 10(7.4%)   |
|                                 | No 125(92.6%)  |
| Recurrence                      | No 96(71.1%)   |
|                                 | Local pelvic recurrence 30(22.9%) |
|                                 | Others 9(6.7%)  |
| Death                           | Yes 17(12.6%)  |
|                                 | No 118(87.4%)  |

Figures

**Figure 1**

A

B

Disease free survival (A) and overall survival (B) in LGESS
Figure 2

Overall survival by cytoreductive surgery for relapse in LGESS
Figure 3

Disease free survival by lymphovascular invasion (A) and overall survival by menopausal status (B) in LGESS.