



## Research Article

# Evaluation of Different Treatment Modalities on Survival of 135 Patients with Low-Grade Endometrial Stromal Sarcoma

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### Abstract

**Background:** To evaluate the influence of different treatment modalities on 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:** The median follow-up duration was 52 months (3-342 months). Two patients received fertility-sparing surgery while 133 patients received hysterectomy. One hundred and nine (80.7%) patients received ovariectomy, 73 (54.1%) patients had lymphadenectomy and 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 ( $p < 0.05$ ) although the complication rate was about 10.3%. Multivariate analyses 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;  $p = 0.015$ ).

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**Citation:** Wang H, Liang S, Feng Z, Xia L, Zhu J, et al. (2020) Evaluation of Different Treatment Modalities on Survival of 135 Patients with Low-Grade Endometrial Stromal Sarcoma. J Reprod Med Gynecol Obstet 5: 045.

**Received:** April 13, 2020; **Accepted:** April 30, 2020; **Published:** May 07, 2020

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**Conclusion:** Hysterectomy may be proposed as the standard treatment for LGESS. Surgery for replese was an acceptable method to improve overall survival.

**Keywords:** Low-grade endometrial stromal sarcoma; Prognosis; Treatment

### List of abbreviations

ESS: Endometrial stromal sarcoma

UUS: Undifferentiated Uterine Sarcoma

LGESS: Low-Grade Endometrial Stromal Sarcoma

HGESS: High-Grade Endometrial Stromal Sarcoma

WHO: World Health Organization

FIGO: International Federation of Gynecology and Obstetrics

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

PET-CT: Positron Emission Tomography-Computed Tomography

SPSS: Statistic Package for Social Science

### Background

Uterine sarcomas represent 8% of all uterine malignancies and Endometrial Stromal Sarcoma (ESS) accounts for approximately 20% of all uterine sarcomas [1]. There are 2 categories of ESS: Low-Grade Endometrial Stromal 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 [5,6]. However, the roles of other therapies such as ovariectomy, lymphadenectomy, and postoperative adjuvant therapy, remain controversial [7-9]. In the present study, we retrospectively reviewed the treatments given to patients with LGESS to evaluate the efficacy of different treatment modalities on survival. The associations between clinicopathologic variables and survival were also evaluated.

### Methods

The Review Board of Fudan University Shanghai Cancer Center approved the study. The study included the LGESS patients from January 2006 to December 2018 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). Two patients who wanted to preserve the fertility received hysteromyoma. The surgery generally included total hysterectomy ± bilateral salpingo-oophorectomy ± lymphadenectomy. For patients with multiple metastases, cytoreductive surgeries were performed. Hormone therapy comprised Megestrol acetate 160 mg/d or Letrozole 2.5mg/d or Medroxyprogesterone acetate 500 mg/d. 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

for 3-6 cycles: cisplatin 50 mg/m<sup>2</sup> (d1) + cyclophosphamide 500 mg/m<sup>2</sup> (d1) + epirubicin 60 mg/m<sup>2</sup> (d1), or gemcitabine 900 mg/m<sup>2</sup> (d1, 8) + docetaxel 100 mg/m<sup>2</sup> (d8), or doxorubicin 60 mg/m<sup>2</sup> (d1) + ifosfamide 1.5 g/m<sup>2</sup> (d1-4).

Patient clinicopathologic factors included 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. When the recurrence was suspected, the patients would be examined by needle biopsy, or Computed Tomography (CT), or Magnetic Resonance Imaging (MRI), or Positron Emission Tomography-Computed Tomography (PET-CT) 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 the first 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 the first 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, and compared using the log rank test. Univariate and multivariate Cox regression analyses were performed to analyze prognostic factors. A p-value less than 0.05 were considered statistically significant.

## Results

### Clinicopathologic factors and treatment modalities of LEGSS patients

A total of 135 LEGSS patients were retrospectively analyzed. 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. Thirty (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 LEGSS 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 surgery.

### 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 (Figure 1A). The 5-year and 10-year overall survival rates were 88.0% and 79.8%, respectively (Figure 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). Twenty-nine 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. So the surgery was related to improved overall survival (p<0.05, Figure 2). The main surgical complications for recurrent diseases were as follows: intestinal fistula (n=2), and urinary fistula (n=1). The complication rate was 10.3%. At the time of last follow up, 17 patients had died of cancer-related diseases.

Characteristics	n (%)
<b>Age (years)</b>	
Median (range)	41.2 (19-65)
≤50	112 (83.0%)
>50	23 (17.0%)
<b>Menopausal status</b>	
Premenopausal	118 (87.4%)
Postmenopausal	17 (12.6%)
<b>Patient's symptom</b>	
No	84 (62.2%)
Abnormal vaginal bleeding	37 (27.4%)
Abdominal pain	12 (8.9%)
Others	2 (1.5%)
<b>Laparoscopic myomectomy</b>	
Yes	30 (22.2%)
No	105 (77.8%)
<b>Tumor size</b>	
≤5cm	39 (28.9%)
>5cm	96 (71.1%)
<b>Muscular infiltration</b>	
≤1/2	32 (23.7%)
>1/2	103 (76.3%)
<b>Lymphovascular invasion</b>	
Yes	33 (24.4%)
No	102 (75.6%)
<b>Lymph node metastasis</b>	
Yes	9 (6.7%)
No	126 (92.6%)
<b>FIGO stage</b>	
I	108 (80.0%)
II	13 (9.6%)
III	12 (8.9%)
IV	2 (1.5%)

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

Characteristics	n (%)
<b>Hysterectomy</b>	
Yes	133 (98.5%)
No	2 (1.5%)
<b>Lymphadenectomy</b>	
Yes	73 (54.1%)
No	62 (45.9%)
<b>Ovariectomy</b>	
Yes	109 (80.7%)
No	26 (19.3%)
<b>Adjuvant therapy</b>	
No	52 (38.5%)
Hormonal therapy	38 (28.1%)
Radiotherapy and hormonal therapy	22 (16.3%)
Chemotherapy and hormonal therapy	23 (17.0%)
<b>Residual disease</b>	
Yes	10 (7.4%)
No	125 (93.3%)
<b>Recurrence</b>	
No	96 (71.1%)
Local pelvic recurrence	30 (22.2%)
Others	9 (6.7%)
<b>Death</b>	
Yes	17 (12.6%)
No	118 (87.4%)

Table 2: Comparison of reproductive data between both study groups.

### Prognostic 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;  $p = 0.038$ ) (Figure 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;  $p = 0.048$ ) (Figure 3B). When we further assessed different treatment methods and prognostic factors in 108 LGESS patients with stage I, we still found the similar results: lymphovascular invasion was associated with disease free survival and menopausal status was related to overall survival at multivariate analyses.

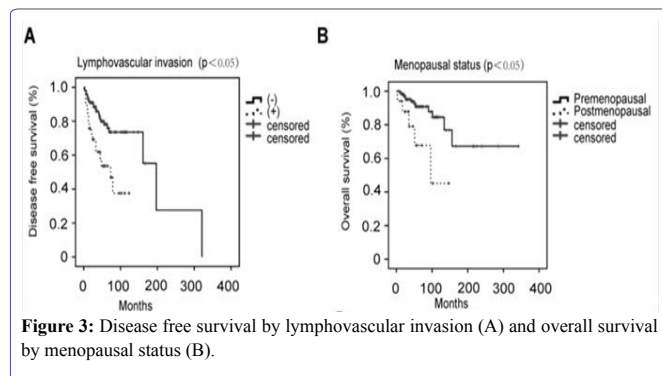


Figure 3: Disease free survival by lymphovascular invasion (A) and overall survival by menopausal status (B).

### Discussion

Endometrial stromal sarcomas were rare uterine malignancies that might manifest through abnormal uterine bleeding and pelvic mass [6]. 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 [10]. A consensus review suggested morcellation should be avoided [1]. 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 [6]. It was also reported that fertility-sparing surgery may be considered for early-stage LGESS patients [11,12]. Rather, some study suggested that the

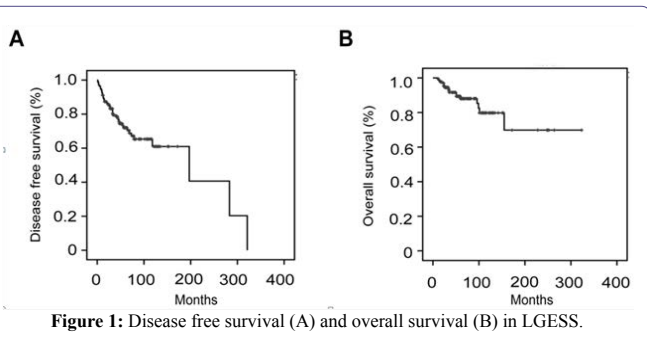


Figure 1: Disease free survival (A) and overall survival (B) in LGESS.

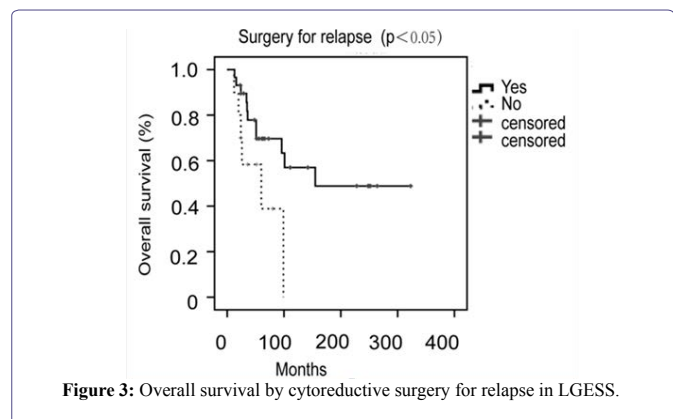


Figure 3: Overall survival by cytoreductive surgery for relapse in LGESS.

removal of the adnexa might be helpful to decrease the risk of recurrence [13]. In our study, 2 patients received fertility-sparing surgery with postoperative hormone therapy 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 (54.1%) patients received lymphadenectomy and only 9 (6.7%) 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 and bilateral salpingo-oophorectomy 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 lymphadenectomy in LGESS patients without lymphatic metastasis.

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 [9,20]. Cade's study did not regard primary adjuvant progestogen as a survival benefit [21]. Although most previous articles recommended postoperative hormone therapy, our paper did not find hormone therapy was associated with survival due to limited data. The recurrent rate increased with the development of the stage in our research. 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 ( $p<0.05$ ) although the complication rate was about 10.3%. 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. Preoperative intestinal and urinary preparation may help to reduce the rate of the complications.

Bai reported that the 5-year relapse free survival and overall survival rates were 66.1% and 95.8% in LGESS [23]. In our study, the 5-year disease free survival and overall survival rates were 72.0% and 88.0% and the 10-year disease free survival and overall survival rates were 61.0% and 79.8%. 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 analyses, 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.

## Conclusion

In conclusion, 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.

## 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.

## Funding

This work was supported by Science and Technology Commission of Shanghai Municipality (grant no. 11ZR1407700) of Yan Huang and National Natural Science Foundation of China (grant no. 81202051) of Yan Huang.

## 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.

## Acknowledgement

We would like to thank all the doctors, nurses, patients, and their family members for their kindness to support our study.

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