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ORIGINAL ARTICLE

Hormone therapy following surgery in low-grade endometrial stromal sarcoma: Is it related to a decrease in recurrence rate?

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Abstract

Background: Low-grade endometrial stromal sarcoma (LGESS) is, in most cases, a slow-growing malignancy; however, it is related with high recurrence rates. The aim of this study is to determine which factors may be associated with the recurrence rate of LGESS.

Methods: The clinicopathological features and treatment options in 37 patients with LGESS were evaluated.

Results: All patients underwent the hysterectomy and bilateral salpingo-oophorectomy. Additionally, lymphadenectomy was performed in 56.8% (n = 21) of the patients. Among the patients who underwent lymphadenectomy, 14.3% (n = 3) had lymph node metastasis. The disease was limited to the uterus in 75.7% of patients. Treatment following surgery was radiotherapy in three patients, chemotherapy in seven patients, hormone therapy in 12 patients, and chemotherapy plus hormone therapy in one patient. Megestrol acetate was used in all patients who received hormone therapy. Median follow-up time was 96 months. The 5-year disease-free survival and disease-specific survival were 72% and 97%, respectively. The recurrence rate was 27%. Only hormone therapy following surgery was significantly associated with a lower recurrence rate, even in patients with stage 1 disease. None of the patients treated with hormone therapy following surgery had recurrence, whereas recurrence occurred in 38.5% of the patients who underwent surgery only ($p = 0.039$).

Conclusion: Hormone therapy after surgery should be considered a viable option for decreasing the LGESS recurrence rate, regardless of the disease stage.

Keywords: Endometrial stromal sarcoma; Low grade; Lymphadenectomy; Megestrol acetate

1. INTRODUCTION

Endometrial stromal sarcoma (ESS) constitutes 16% to 21% of all uterine sarcomas—rare tumors that account for 3% of all uterine malignancies.[1–3] Endometrial stromal tumors that originate from endometrial stroma are subdivided histopathologically into the following four groups based on 2014 WHO classification:[4] endometrial stromal nodule; low-grade ESS (LGESS); high-grade ESS; undifferentiated uterine sarcoma. LGESS is diagnosed based on the absence of nuclear atypia/pleiomorphism, good differentiation, a mitotic index <10 mitoses per 10 high-power fields in specimens stained with hematoxylin and eosin.[5] The immunochemical analysis shows especially CD10 positivity and h-caldesmon negativity.[5] Although a significant proportion of LGESS holds a JAZF1-SUZ12 (formerly named JAZF1-JJAZ1) gene fusion, molecular analysis is not routinely mandatory for the diagnosis of LGESS.[6,7] Molecular analysis can be used to classify difficult cases.

LGESS is most commonly encountered in premenopausal women with abnormal uterine bleeding.[8] The initial treatment is surgery,[9] but reports on the optimal extent of surgery, the utility of lymphadenectomy, and the necessity of adjuvant therapy are inconsistent.[10–13] Although LGESS is associated with a higher survival rate than other sarcomas, it has been reported that 37% to 50% of patients have recurrence during the late period of the disease.[9,11,14] Tumor size, tumor grade, stage, menopausal status, age and type of treatment, and prognostic significance are reported for each of them.[13,15,16] The current study aimed to determine the clinical–pathological factors that are associated with recurrence rate in the LGESS.

2. METHODS

Data of 61 patients treated for histopathologically proven ESS between January 1985 and March 2016 at the gynecologic oncology clinic of our institution were obtained from an electronic database and patient files. Among the patients, six patients with unspecified grade sarcomas, 17 with high-grade or undifferentiated sarcomas, and one with follow-up for <3 months were excluded. The study was completed with 37 patients with LGESS. All patients signed an informed consent that allows the participating institution to use their clinical data. IRB approval was obtained before the study.

Surgery was the initial therapy in all patients. The decision about performing lymphadenectomy was made according to

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the discretion of the senior surgeon. Lymphadenectomy was performed via sampling or via skeletonizing pelvic and para-aortic vessels, at the discretion of senior surgeon according to findings such as serious systemic medical history and obesity. Experienced gyneco-pathologists analyzed all specimens that are obtained. Tumor size was defined as maximum tumor diameter. The stage is modified according to 2009 FIGO staging criteria. Decisions about the use of adjuvant therapy and the adjuvant therapy regime following surgery were made by the senior surgeon and the gynecologic oncology counsel. In patients who received hormone therapy following surgery, it was administered for two additional years.

Clinical response was defined as follows: (1) Complete response: complete disappearance of all target and nontarget lesions, and absence of new lesions; (2) progressive disease (PD): ≥20% increase in the maximum diameter of the target lesion, the appearance of ≥1 new lesions, or progression of any nontarget lesion; according to the assessment made at the first-month posttreatment.[17] Patients who had a complete clinical response to initial treatment were followed-up every 3 months for the first 2 years, semi-annually for the next 3 years, and annually thereafter. Pelvic examination, abdomino-pelvic ultrasonography, complete blood count, and blood chemistry were performed at every follow-up visit. Follow-up chest radiograph was performed yearly, but in cases of clinical suspicion, it was used when needed. Thoracic and/or abdominal computerized tomography was also performed when needed.

The time from surgery to recurrence or last follow-up visit was defined as disease-free survival (DFS) and the time from surgery to death because of the disease or last follow-up visit was defined as disease-specific survival (DSS). The time from recurrence to death or last follow-up visit was defined as post-recurrence survival. The recurrence distal to the pelvic inlet was defined as pelvic recurrence; recurrence between the pelvic inlet and diaphragm was defined as abdominal recurrence; and all other types of recurrence, including liver parenchyma, lung, and bone, was defined as extraabdominal recurrence. Metastatic localization at the time of diagnosis was defined according to the same criteria.

Statistical analysis was performed using SPSS for Windows v.11.5 (SPSS, Inc., Chicago, IL). Categorical variables were compared using the χ^2 test or Fisher's Exact test, as appropriate. Survival analysis was performed using the Kaplan–Meier method. The level of statistical significance was set at $p < 0.05$.

3. RESULTS

Median age at the time of diagnosis was 47 years (range: 34-61 years) and 78% of the patients were at premenopausal stage. The most common symptom was abnormal uterine bleeding (51.4%). None of the patients in the study had pelvic radiotherapy history. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. In addition, lymphadenectomy was performed in 21 (56.8%) patients. Among those patients, all but one underwent both pelvic and paraaortic lymphadenectomy and one patient underwent only pelvic lymphadenectomy. The median number of removed lymph nodes was 46 (range: 16-120).

Tumor diameter was ≤5 cm in 40.5% (n = 15) of the patients. In all, four patients had serosal involvement. Among the patients who underwent lymphadenectomy, three (14.3%) had lymph node metastasis. One patient had only pelvic lymph node metastasis and two had pelvic and para-aortic lymph node metastasis. The disease was confined to the uterus in 75.7% (n = 28) of the patients. In total, four patients had stage 2 disease versus five patients with stage 3 disease. None of the patients had stage 4 disease. Maximal cytoreduction (no residue) is obtained in all patients. Patient's clinical and pathological findings are shown in Table 1.

Among the patients, 23 received treatment following surgery, as follows: radiotherapy: n = 3; chemotherapy: n = 7; hormone therapy: n = 12 patients; chemotherapy plus hormone therapy: n = 1. Chemotherapy agents used were adriamycin in seven patients, and a combined regimen of ifosfamide, mesna, and adriamycin in one patient. Megestrol acetate was used in all patients who received hormone therapy.

The 5-year DFS and 5-year DSS rates were 72% and 97%, respectively (Figs. 1 and 2). In all, 36 patients had a complete response to initial therapy and one patient had PD. The median duration of follow-up was 96 months (range: 8-277 months). During follow-up, ten (27%) patients had disease recurrence and two (5.4%) died due to disease, of which one had PD and died 11 months after initial diagnosis and one had disease recurrence 131 months after surgery and died 2 months later. Median time to recurrence was 29 months (range: 16-180 months). Among the patients with recurrence, localization was pelvic in two patients, pelvic and abdominal in five, abdominal and extraabdominal (lung) in two, and extra-abdominal (bone) in one patient.

Table 1

Clinicopathological features of patients with LGESS

Characteristics	n (%)
Menopausal status	
Premenopausal	29 (78)
Postmenopausal	7 (19)
Not reported	1 (3)
Presenting symptoms	
Abnormal uterine bleeding	19 (51.4)
Abdominal swelling	6 (16.2)
Postmenopausal bleeding	5 (13.5)
Pelvic pain	3 (8.1)
Incidental	1 (2.7)
Postoperative pathologic diagnosis	1 (2.7)
Not reported	2 (5.4)
Stage	
1	28 (75.7)
1A	11 (29.7)
1B	8 (21.6)
Not differentiated (1A or 1B)	9 (24.3)
2	4 (10.8)
2A	1 (2.7)
2B	3 (8.1)
3	5 (13.5)
3A	1 (2.7)
3B	1 (2.7)
3C	3 (8.1)
Tumor diameter	
≤5 cm	15 (40.5)
>5 cm	10 (27)
Not reported	12 (32.4)
Serosal involvement	
Absent	21 (56.8)
Present	4 (10.8)
Not reported	12 (32.4)
Cervical involvement	
Absent	31 (83.8)
Present	3 (8.1)
Not reported	3 (8.1)
Adnexal involvement	
Absent	34 (91.9)
Present	3 (8.1)
Abdominal involvement	
Absent	35 (94.6)
Present	2 (5.4)
Lymph node metastasis[a]	
Absent	18 (85.7)
Present	3 (14.3)

LGESS = low-grade endometrial stromal sarcoma.

[a]Among the patients performed lymphadenectomy (n:21).

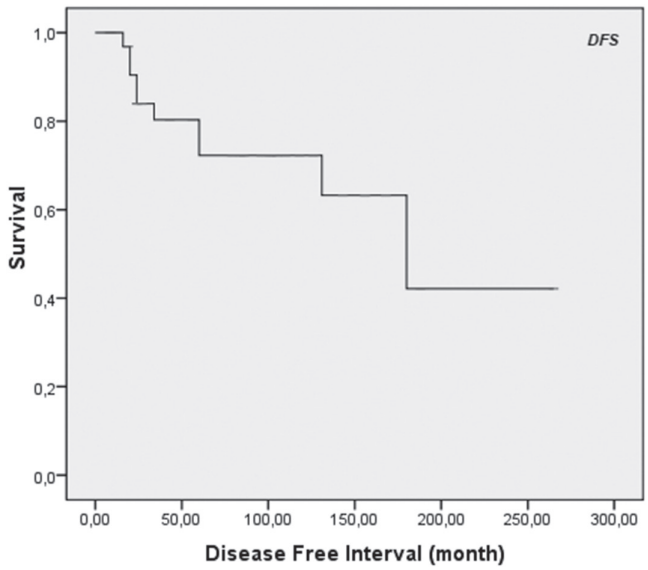

Fig. 1 The disease-free survival (DFS) curve of entire cohort.

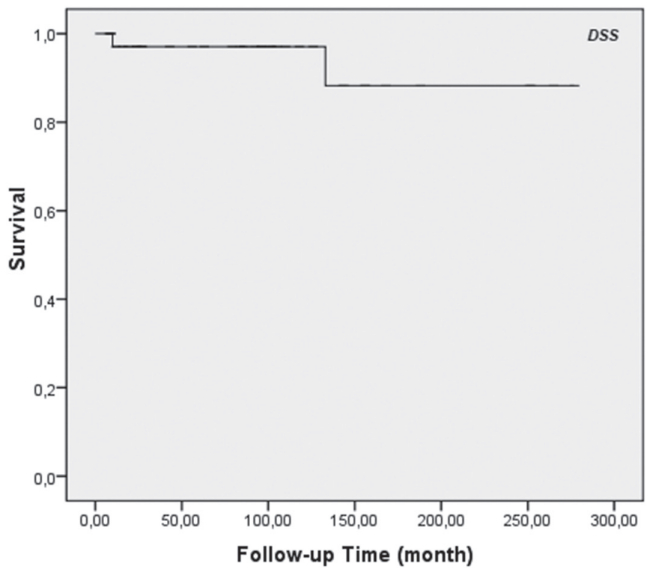

Fig. 2 The disease-specific survival (DSS) curve of entire cohort.

Among the clinical, surgical, and pathological factors, only adjuvant hormone therapy was significantly associated with a decrease in the recurrence rate (Tables 2 and 3). Recurrence occurred in 14.3% of the patients who underwent lymphadenectomy and in 46.7% who did not undergo lymphadenectomy, but the difference was not significant (p = 0.058). There was not a significant difference in the recurrence rate between the patients who underwent surgery only, and those who underwent radiotherapy or chemotherapy following surgery. Among the three patients with the recurrence who had received postsurgery radiotherapy, one had a pelvic recurrence. None of the patients treated with hormone therapy after surgery had recurrence, whereas recurrence occurred in 38.5% of the patients who underwent surgery only; the difference was significant (p = 0.039). There was not a significant difference in the distribution of disease stage between the patients treated with and without hormone therapy (p = 0.432). Subgroup analysis of the stage 1 LGESS patients showed that the addition of lymphadenectomy to surgical treatment was not significantly associated with recurrence (p = 0.209). Hormone therapy after surgery was significantly associated with recurrence compared with surgery only (p = 0.05).

Table 2

Association between clinicopathological features and recurrence in all cohort

	Presence of recurrence	
Clinicopathological features	**n (%)**	***p***
Age		
≤50 y	6 (25)	0.700
>50 y	4 (33.3)	
Menopause status		
Premenopausal	7 (24.1)	0.322
Postmenopausal	3 (50)	
Stage		
1	7 (25.9)	0.686
2 and 3	3 (33.3)	
Tumor diameter		
≤5 cm	5 (33.3)	0.061
>5 cm	0 (0.0)	
Uterine serosal involvement		
Absent	3 (14.3)	0.099
Present	2 (66.7)	
Cervical involvement		
Absent	6 (20)	0.523
Present	1 (33.3)	
Adnexal involvement		
Absent	9 (27.3)	1.000
Present	1 (33.3)	
Abdominal involvement		
Absent	10 (29.4)	1.000
Present	0 (0.0)	
Lymph node metastasis		
Absent	2 (11.1)	0.386
Present	1 (33.3)	

*p < 0.05 is statistically significant.

Salvage therapy in patients with recurrence included surgery plus chemotherapy (n = 2), surgery plus chemotherapy and hormone therapy (n = 2), hormone therapy only (n = 1), surgery plus radiotherapy and hormone therapy (n = 2), and surgery plus hormone therapy (n = 2). One patient with lumbar vertebral recurrence was referred for neurosurgery but was lost to follow-up. In total, eight patients had a complete response to salvage therapy. One patient with the pelvic and abdominal recurrence who had been disease free for 131 months died 2 months after starting salvage chemotherapy. The postrecurrence survival of patients with recurrence was 72 months (range: 2-247 months).

4. DISCUSSION

LGESS is, in most cases, a slow-growing malignancy and although its prognosis is generally good, 24% to 50% of patients experience late recurrence; however, it remains unclear which factors affect recurrence.[9,11,14,18,19] LGESS patients have a 5-year DSS >95%, but it was reported that 5-year DFS is 66% to 93%.[20,21] The lower DFS rate might have been due to the fact that although LGESS is an indolent tumor, the recurrence rate can be as high as 50% and the majority of such cases are late recurrence.[9,13,20] In the current study, the recurrence rate was 27%. The overall 5-year DFS and 5-year DSS rates were 72% and 97%, respectively; and as reported earlier,[9,13,20] in the current study most common (70%) recurrence sites were pelvis and abdomen.

The cornerstone of the treatment of LGESS is surgery, but there is a lack of consensus concerning the optimal extent of surgery. Total hysterectomy with bilateral salpingo-oophorectomy is highly recommended as a standard treatment for LGESS, even in cases of stage 1 disease.[8,9,13,18,20] Although ovarian preservation has no effect on OS, it is associated with an increased risk of relapse and poor DFS, and, therefore, should be considered

Table 3

Association between initial therapy options and recurrence in all cohort

Initial therapy options	Presence of recurrence n (%)	*p*
Initial surgery type		
TAH + BSO	7 (46.7)	0.058
TAH + BSO + lymphadenectomy	3 (14.3)	
Only surgery and surgery with adjuvant therapy		
Only surgery	5 (38.5)	0.440
Surgery with adjuvant therapy	5 (21.7)	
Only surgery and surgery with adjuvant radiotherapy		
Only surgery	5 (38.5)	0.200
Surgery with only adjuvant radiotherapy	3 (100)	
Only surgery and surgery with adjuvant chemotherapy		
Only surgery	5 (38.5)	1.000
Surgery with only adjuvant chemotherapy	2 (28.6)	
Only surgery and surgery with adjuvant hormone therapy		
Only surgery	5 (38.5)	0.039*
Surgery with only adjuvant hormone therapy	0 (0.0)	

BSO = Bilateral salpingo-oophorectomy; TAH = Total abdominal hysterectomy.
*$p < 0.05$ is statistically significant.

in only highly selected patients.[9,13,22] ESS has a strong predilection for local lymphatic invasion.[13] The incidence of lymph node metastasis among all patients with LGESS who undergo lymphadenectomy is 7% to 30% versus 5% (range: 0%-16%) in those with clinically apparent early stage disease.[23–25] Even though underlying reasons for performing lymphadenectomy that was recommended by 2009 FIGO were high rates of lymph node metastasis and providing an opportunity for evaluation of the real stage, the benefit of lymphadenectomy remains unclear.

Research has shown that lymphadenectomy has no therapeutic benefit in patients with LGESS and that there is not a significant difference in DFS or OS in patients treated with and without lymphadenectomy, regardless of disease stage.[8,9,11,20,25–27] Tanz et al.[8] reported that DFS did not differ between lymph node metastasis-positive and negative patients who underwent lymphadenectomy. Chan et al.[25] observed that although lymphadenectomy had no effect on DSS, lymph node metastasis was associated with poorer DSS in patients who underwent lymphadenectomy. Consideration of lymphadenectomy is recommended in LGESS to obtain more correct prognostic information owing to the determination of real stage.[20,25] In the current study, the incidence of lymph node metastasis was 14% and, as previously reported, lymphadenectomy and lymph node status were not significantly associated with recurrence, regardless of disease stage.

There is a lack of consensus concerning the necessity, benefits, and type of adjuvant therapy for treating LGESS. Feng et al.[22] initially observed that multiple-agent chemotherapy might improve recurrence-free survival in patients with early-stage LGESS, but following multivariant analysis, such an effect was not noted. Chemotherapy, radiotherapy, or both after definitive surgery for LGESS had no effect on survival or recurrence.[12,20,28] Weitmann et al.[29] observed that adjuvant radiotherapy can decrease the risk of local recurrence ESS but evidence of this beneficial effect in patients with LGESS is lacking. The majority of LGESS tumors express estrogen and progesterone receptors; therefore, LGESS is considered to be hormone sensitive.[30]

The most commonly used hormone therapies for LGESS are progestin agents, especially megestrol acetate and the aromatase inhibitor Letrozole.[15,30] Additionally, there are some case reports describing the use of leuprolide acetate.[31,32] Hormone therapy is recommended on the basis of hormone receptor status.[18] Significantly lower recurrence rates were noted in patients who received hormone therapy following surgery compared to patients who underwent only surgery.[19,33] Krauss et al.[15] also reported that the effect of hormone therapy is observed even in patients with stage 1 disease. Optimal age for women to begin hormone therapy remains controversial, it should be continued to use during the 2 years in the absence of the disease or lifelong.[33] In the present study, only hormone therapy (megestrol acetate) after surgery was significantly associated with a decrease in the recurrence, even in cases of stage 1 disease, and none of the patients who received megestrol acetate had a recurrence.

The current study's primary limitation is its retrospective design. Additionally, uterine- and ovarian-sparing treatments were not evaluated because ovarian preservation is not the preferred therapy for LGESS in our department and none of the patients desired fertility preservation. In contrast, the present study included a large number of patients with LGESS—a rarely seen tumor. Also, long-term outcomes were reported based on a median follow-up time of 96 months.

In conclusion, LGESS is a rare uterine tumor with a generally good prognosis, despite a high probability of recurrence. Hysterectomy with bilateral salpingo-oophorectomy is the cornerstone of treatment. Only hormone therapy following surgery is associated with a decrease in the recurrence rate, even in patients with stage 1 disease. Additional multicenter randomized controlled studies are required to more clearly determine the best treatment options for maximizing survival in patients with LGESS.

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