Primary characteristics and outcomes of newly diagnosed low-grade endometrial stromal sarcoma

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HIGHLIGHTS

⇒ Low-grade endometrial stromal sarcoma is a rare disease, limiting large-scale analyses of outcomes.
⇒ Systematic lymphadenectomy is not therapeutic or beneficial in determining lymph node metastasis.
⇒ Early-stage disease is less likely to recur; disease-specific survival is not dependent on stage.

ABSTRACT

Objective To assess potential predictive variables for nodal metastasis and survival outcomes in patients with newly diagnosed, low-grade endometrial stromal sarcoma.

Methods We performed a single-institution, retrospective analysis of consecutive patients with newly diagnosed, low-grade endometrial stromal sarcoma who presented between January 1, 1980 and December 31, 2019 and underwent hysterectomy at our institution or presented within 3 months of primary surgery elsewhere before recurrence. Patients who presented to our institution only at recurrence were excluded. Patients with <3 months of follow-up were excluded from survival analyses.

Results We identified 127 consecutive patients for analysis. Median age at diagnosis was 48 years (range 19–88 years); 91 (74.6%) of 127 were pre-menopausal; and 74 (58.3%) of 127 had uterine-confined, stage I tumors. Of 56 patients (44.1%) who underwent lymph node sampling, 10 (17.9%) had nodal metastasis. Of the 10 with nodal metastasis, 1 (10%) did not have lymphadenopathy or extra-uterine disease, 4 (40%) had lymphadenopathy only, 1 (10%) had extra-uterine disease only, and 4 (40%) had both. Among the 29 patients without apparent extra-uterine disease or gross lymphadenopathy, there was one occult lymph node metastasis (3.4%). Gross lymphadenopathy at time of surgery was predictive for lymph node metastasis (p<0.001). Median follow-up was 69 months (range 4–336) for the 95 patients included in the survival analyses. The 5-year progression-free survival and disease-specific survival rates were 79.8% and 90.8%, respectively. Patients with stage I tumors had longer progression-free survival than those with stage II–IV disease (p<0.001); there was no difference in disease-specific survival (p=0.63). Post-operative observation versus adjuvant therapy with hormone blockade or radiation therapy did not result in progression-free survival differences for stage I or completely resected stage II–IV disease (p=0.50 and p=0.81, respectively). Similarly, there was no disease-specific survival difference for completely resected stage II–IV disease (p=0.3).

Conclusions Lymph node dissection in patients with low-grade endometrial stromal sarcoma should be reserved for those with clinically suspicious lymphadenopathy. Disease stage correlated with progression-free survival but not disease-specific survival. Post-operative therapy did not improve progression-free survival or disease-specific survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Low-grade endometrial stromal sarcoma is a rare disease with debatable treatment recommendations regarding lymphadenectomy, oophorectomy, and adjuvant therapy for completely resected disease.

WHAT THIS STUDY ADDS

⇒ Our results showed that lymph node dissection in patients with low-grade endometrial stromal sarcoma should be reserved for those with clinically suspicious lymphadenopathy. Disease stage correlated with progression-free survival but not disease-specific survival. Adjuvant therapy did not improve survival, and ovary retention was not associated with recurrence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, AND/OR POLICY

⇒ Our study findings can assist practitioners in the clinical management of low-grade endometrial stromal sarcoma—a rare disease with debatable management strategies.

INTRODUCTION

Endometrial stromal sarcoma is a rare mesenchymal tumor, accounting for less than 1% of uterine cancers; however, it is the second most common uterine sarcoma, after leiomyosarcoma, comprising 17–25% of cases.[1 2] Endometrial stromal tumors are classified into four histopathologic entities—endometrial stromal nodules, low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma, and undifferentiated uterine sarcomas.[3] Low-grade

endometrial stromal sarcoma is generally characterized by an indolent course and favorable prognosis, with a 5-year overall survival rate of >90%.[1 2]

Low-grade endometrial stromal sarcoma appears grossly as tan-to-yellow confluent masses involving the endomyometrium. Histologically, sheets of small, cytologically uniform spindle cells associated with delicate vasculature and low mitotic activity resembling proliferative endometrial stroma infiltrate the myometrium and demonstrate frequent lymphovascular space invasion. Low-grade endometrial stromal sarcoma commonly expresses CD10, estrogen receptor, and progesterone receptor, and frequently harbors recurrent chromosomal translocations resulting in gene fusions, the most common of which are *JAZF1-SUZ12* fusions.[1]

Patients with low-grade endometrial stromal sarcoma commonly present with abnormal uterine bleeding, pelvic pain, or dysuria, but some patients are asymptomatic at diagnosis.[2] The primary treatment of choice for low-grade endometrial stromal sarcoma is surgical resection with total hysterectomy. Bilateral salpingo-oophorectomy is generally recommended, although debatable for all patients. The overall rate of lymph node metastases ranges up to 30%, but the clinical benefit of lymphadenectomy is controversial.[1 4] Patients with stage I, uterine-confined tumors are generally observed after hysterectomy. Adjuvant therapy for patients with extra-uterine disease, after resection, typically includes discretionary estrogen blockade and/or external-beam radiation therapy.[4] Chemotherapy has not been shown to improve overall survival.[5]

Given the rarity of low-grade endometrial stromal sarcoma and ongoing controversial treatment recommendations regarding lymphadenectomy and oophorectomy, we examined cases of low-grade endometrial stromal sarcoma from our tertiary care center. Our primary outcome was the rate of overall and occult lymph node metastasis. We also evaluated the predictive value of lymph node sampling based on gross appearance at surgery and other pathologic variables on lymph node metastasis. Additionally, we explored the relationship of multiple clinicopathologic features, including stage and adjuvant treatment after resection, with patient survival.

METHODS

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement was used to guide study design and result reporting.[6] After institutional review board approval, all consecutive patients with endometrial stromal sarcoma treated or evaluated at Memorial Sloan Kettering Cancer Center between January 1, 1980 and December 31, 2019 were identified. Patients with low-grade endometrial stromal sarcoma who had undergone hysterectomy with or without adnexectomy were eligible for the study. Patients with endometrial stromal nodules, high-grade endometrial stromal sarcoma, or undifferentiated uterine sarcoma were ineligible. Only patients presenting in the primary setting were included in analyses.

We excluded patients who presented to our institution only at the time of recurrence or >3 months after their initial surgery elsewhere without recurrence. Patients with low-grade endometrial stromal sarcoma arising in extra-uterine sites or diagnosed after myomectomy without evidence of completion hysterectomy were also excluded. We previously reported the incidence of lymph node and adnexal metastasis in endometrial stromal sarcoma at our institution between 1980 and 2009.[7] Medical records from this prior publication were re-reviewed for this study. Pathology for the cases included in our prior publication were re-reviewed by an expert gynecologic pathologist using modern criteria for low-grade endometrial stromal sarcoma. Since then, all cases have been reviewed by expert pathologists using the same criteria at the time of presentation but were not again re-reviewed.

Clinical and pathology data, operative findings, adjuvant treatments, and dates of recurrence or progression, death, or last follow-up were collected from the electronic medical records. Stage was retrospectively assigned using the International Federation of Gynecology and Obstetrics (FIGO) 2018 classification system for uterine sarcomas.[2] For comparative analyses, uterine tumor size was categorized using a threshold of 5 cm.[8] Occult lymph nodes were considered those positive for metastatic disease on final pathology without gross lymphadenopathy or extra-uterine disease at the time of surgical resection. Gross lymphadenopathy was considered independent and separate from gross extra-uterine or peritoneal disease. Progression-free survival was defined as the time from surgery to the date of disease progression, death, or last follow-up. Disease-specific survival was defined as the time from initial surgery to the date of death from disease, excluding death from other causes, or last follow-up.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, New York, USA). Valid percentages were reported to reflect distributions of available data. Potential predictive variables for lymph node metastasis were evaluated using X^2 and Fisher's exact tests. For survival analyses, patients with less than 3 months of follow-up were excluded and cohort percentage survival at 5 years with standard errors were reported. For survival analyses based on adjuvant therapies, patients with residual disease were excluded. Survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test for multiple variables. Correction for multiple comparisons was not performed due to the small cohort sizes.

RESULTS

Of 229 patients with endometrial stromal sarcoma, 70 were excluded as non-low-grade endometrial stromal sarcoma; 5 had not undergone hysterectomy; 1 had sarcoma arising in endometriosis 20 years after hysterectomy; and 26 presented with recurrent disease at the time of evaluation at our institution. This left 127 patients for analysis.

Clinical, pathology, and surgical characteristics are listed in Table 1. Median age at diagnosis was 48 years (range 19–88). Median body mass index was 24.7 kg/m^2 (range 18.4–54.5). Ninety-one patients (74.6%) were pre-menopausal. Seventy-four patients (58.3%) had uterine-confined, stage I disease; 23 (18.1%) had stage II disease; 17 (13.4%) had stage III disease; and 13 (10.2%) had stage IV disease.

Lymph node evaluation details are listed in Table 2. Fifty-six patients underwent lymph node assessment at initial surgery—33 (58.9%) of the pelvic lymph node basin only, 4 (7.1%) of the para-aortic lymph node basin only, and 19 (33.9%) of both. The median number of pelvic and para-aortic lymph nodes removed were 9

Table 1 Baseline characteristics

Characteristics	Evaluable patients (n=127)
Age at diagnosis (years), median (range)	48 (19–88)
Race	
White	99 (86.1%)
Asian	9 (7.8%)
Black	5 (4.3%)
Hispanic	2 (1.7%)
No data	12
BMI at diagnosis (kg/m^2), median (range)	24.7 (18.4–54.5)
Age of menarche (years), median (range)	12 (10–15)
History of OCP use	39/64 (60.9%)
Duration of OCP use (of users) (years), median (range)	3.8 (0.3–15)
Parity	
Nulliparous	30 (25.6%)
Parous	87 (74.4%)
No data	10
Menopausal status	
Pre-menopausal	91 (74.6%)
Post-menopausal	31 (25.4%)
No data	5
Age of menopause (if post-menopausal) (years), median (range)	52 (41–58)
History of HRT use prior to diagnosis of LGESS	8/78 (10.3%)
Duration of HRT use (of users) (years), median (range)	10 (7–10)
History of breast cancer	11/119 (9.2%)
History of tamoxifen use	5/121 (4.1%)
History of diabetes mellitus	4/121 (3.3%)
BSO prior to diagnosis	2 (1.6%)
Uterine tumor size (cm), median (range)	5.5 (0.7–15.8)
FIGO stage*	
I	74 (58.3%)
II	23 (18.1%)
III	17 (13.4%)
IV	13 (10.2%)
Presence of LVSI	79/96 (82.3%)
Mitoses, per 10 hpf, median (range)	3 (0–10)
Ovary/ovaries preserved after hysterectomy	10 (7.9%)
Residual tumor after primary surgical resection	17 (13.4%)

For yes/no variables, only 'yes' values are shown.
*2018 FIGO staging system used.
BMI, body mass index; BSO, bilateral salpingo-oophorectomy; FIGO, International Federation of Gynecology and Obstetrics; hpf, high power fields; HRT, hormone replacement therapy; LGESS, low-grade endometrial stromal sarcoma; LVSI, lymphovascular space invasion; OCP, oral contraceptive pills.

(range 1–32) and 5 (range 1–67), respectively. The rate of nodal metastasis was 17.9% (n=10/56). Among the 29 patients without apparent extra-uterine disease or gross lymphadenopathy, one had occult lymph node metastasis (3.4%), which is less than our prior report of 10%.[7] One patient we had reported as having an occult positive lymph node in our prior publication had instead grossly enlarged nodes on surgical exploration, which was not appreciated at the time of our data extraction then and was thus not included in our calculations. This accounts for the discrepancy in the rate of occult nodal metastasis between the current and prior report. There was a significant relationship between grossly enlarged nodes at the time of surgical treatment and the presence of lymph node metastasis (p<0.001). Patients without gross lymphadenopathy or extra-uterine disease had a significantly lower risk of lymph node metastasis than those with lymphadenopathy, extra-uterine disease, or both (p=0.005). Those without gross lymphadenopathy also had a significantly lower risk of lymph node metastasis than patients with lymphadenopathy (p<0.001). The presence of lymphovascular space invasion or uterine tumor size >5 cm was not a significant risk for lymph node metastasis (p=0.57 and p=0.68, respectively).

Survival analyses are detailed in Table 3. Median follow-up was 69 months (5.8 years; range 4–336 months). There were 22 recurrences (23.2%) and 16 deaths (16.8%). Cause of death was unknown for six patients, and four died from other causes, leaving 89 patients assessable for disease-specific survival. The details of patients whose disease recurred and subsequent interventions and outcomes are currently under continued investigation and will be reported in a future publication. The 5-year progression-free survival rate for all patients was 79.8% (SE ±4.4); the 5-year disease-specific survival rate was 90.8% (SE ±3.6). The 5-year progression-free and disease-specific survival rates for stage I tumors were 89.5% (SE ±4.5) and 92.0% (SE ±4.4), respectively. The 5-year progression-free and disease-specific survival rates for extra-uterine, collective stage II–IV disease were 66.0% (SE ±8.1) and 89.0% (SE ±6.0), respectively (Figure 1). Patients with stage I disease had significantly longer progression-free but not disease-specific survival than those with stage II–IV disease (p<0.001 and p=0.63, respectively).

Uterine tumor size, with a threshold of 5 cm for all cases of all stages, was also significantly related to progression-free survival (p=0.043). The FIGO staging system uses this 5 cm cut-off point only for stage I low-grade endometrial stromal sarcoma, and the comparison significance did not hold when stage II–IV disease was excluded (p=0.65). Progression-free survival was also longer for patients without residual disease after surgical resection (p=0.046). As there is no residual disease in stage I tumors, they were excluded in an exploratory analysis of progression-free survival, and the significance did not remain (p=0.84). Additional survival analyses across multiple variables did not confer significant relationships to progression-free survival. Comparing patients by their history of hormone replacement therapy use prior to their diagnosis of low-grade endometrial stromal sarcoma resulted in the only significant disease-specific survival difference (p=0.018). The number of patients with a history of hormone replacement therapy was small, however, and this result is probably negligible without a significant comparison in the progression-free survival analysis. Additionally, this significant p value may be a chance finding due to the multiple comparisons performed.

Table 2 Details from lymph node evaluations

Characteristics	N	Nodal metastasis, n	%	P value
Patients who underwent node sampling	56	10	17.9	
Gross appearance				**<0.001**
No LAD or EUD	29	1	3.4	
LAD without EUD	8	4	50.0	
EUD without LAD	11	1	9.1	
EUD and LAD	8	4	50.0	
Gross appearance				**0.005**
No LAD or EUD	29	1	3.4	
LAD or EUD or both	27	9	33.3	
Gross appearance				**<0.001**
No LAD	40	2	5.0	
LAD	16	8	50.0	
LVSI				0.57
(–) LVSI	7	0	0	
(+) LVSI	42	7	16.7	
Unavailable	7	3	42.9	
Uterine tumor size				0.68
≤5 cm	21	3	14.3	
>5 cm	17	4	23.5	
Unavailable	18	3	16.7	

EUD, extra-uterine disease; LAD, lymphadenopathy ; LVSI, lymphovascular space invasion.

Only six of the 10 patients with retained ovaries had data to assess oncologic outcomes. All six were pre-menopausal, with ages ranging from 19 to 46 years. Tumor size ranged from 1.4 to 11.5 cm, and none had residual disease. Five had stage I disease; one had stage II disease. Only one of these patients developed a recurrence. This patient was a 19-year-old patient with stage II disease. She did receive leuprolide acetate post-operatively and was diagnosed with a lung metastasis 8 months after the initial surgery, which was resected. All of these patients were alive at last follow-up.

Survival analyses by adjuvant therapy for patients with completely resected disease are shown in Online supplemental table 1. All adjuvant medical therapy in those who were rendered free of disease with surgery of any stage was hormonal (megesterol acetate, leuprolide, or an aromatase inhibitor). Cytotoxic therapy was not used in the adjuvant setting in any case. There was a significant relationship between type of adjuvant therapy and progression-free survival for patients with stage I tumors when four general categories of therapy were considered (observation vs radiation therapy alone vs medical therapy alone vs radiation therapy with medical therapy) (p<0.001). However, the 5-year progression-free survival rate was 93.3% (SE ±4.6%) for observation alone compared with 82.8% (SE ±9.1%) for use of any adjuvant therapy in stage I cases (p=0.5). For patients with completely resected stage II–IV disease, there was no significant relationship between the four general categories of therapy and progression-free or disease-specific survival (p=0.31 and p=0.09, respectively). Similarly, there was no progression-free or disease-specific survival difference when comparing observation with any adjuvant therapy (p=0.81 and p=0.32, respectively; Figure 2). Twelve patients had residual disease after surgery, and only two underwent observation. One of these two patients had recurrence but remained alive at the time of this analysis. The remaining 10 patients received post-operative hormonal-based therapies, with a 5-year progression-free survival rate of 56.3% (SE ±16.5%) and 5-year disease-specific survival rate of 87.5% (SE ±11.7%). Comparison of observation versus therapy was not possible in this small cohort of patients left with residual disease.

DISCUSSION

Summary of Main Results

We accrued 33 additional patients over a 10-year period since our institution's prior report on low-grade endometrial stromal sarcoma,[7] highlighting the rarity of this tumor. The overall rate of lymph node metastasis in our study was 17.9%, consistent with our previously reported rate of 19%.[7] Our finding of an occult lymph node metastasis rate based on grossly normal lymph nodes and no extra-uterine disease was 3.4%, less than our prior 10% rate. With an overall rate of lymph node metastasis in all stages of low-grade endometrial stromal sarcoma approaching 20%, it is most clinically useful to understand the role of lymphadenectomy at the time of surgery on tumor recurrence and survival.

Results in the Context of Published Literature

A prior retrospective study suggested that systematic lymph node dissection reduced local recurrences, but the study was too small

Table 3 Results from survival analyses

	PFS				DSS			
Variable	**Patients, n**	**Events, n**	**5-year % (±SE)**	**P value**	**Patients, n**	**Events, n**	**5-year % (±SE)**	**P value**
All	95	22	79.8 (4.4)		89	6	90.8 (3.6)	
Stage				**0.002**				0.21
I	55	6	89.5 (4.5)		50	3	92.0 (4.4)	
II	19	8	72.2 (10.7)		18	0	100	
III	11	3	75.0 (15.3)		11	2	71.4 (17.1)	
IV	10	5	45.0 (16.6)		10	1	87.5 (11.7)	
Stage				**<0.001**				0.63
I	55	6	89.5 (4.5)		50	3	92.0 (4.4)	
II–IV	40	16	66.0 (8.1)		39	3	89.0 (6.0)	
Tumor size, all stages				**0.043**				0.93
≤5 cm	31	3	89.4 (5.8)		31	3	88.6 (6.2)	
>5 cm	35	10	78.0 (7.4)		32	2	90.2 (6.6)	
Tumor size, stage I				0.65				0.29
≤5 cm	23	2	90.7 (6.3)		23	2	90.2 (6.6)	
>5 cm	18	1	100		16	0	100	
Residual tumor, all stages				**0.046**				0.60
No	84	17	82.5 (4.5)		78	5	91.4 (3.7)	
Yes	11	5	58.9 (16.0)		11	1	85.7 (13.2)	
Residual tumor, stage II–IV				0.84				0.75
No	29	11	68.4 (9.4)		28	2	89.9 (6.8)	
Yes	11	5	58.9 (16.0)		11	1	85.7 (13.2)	
Race				0.48				0.91
White	77	19	79.8 (4.9)		71	4	92.5 (3.6)	
Asian	7	0	100		7	0	100	
Black	3	0	100		3	0	100	
Hispanic	2	0	100		2	0	100	
BMI				0.64				0.29
Healthy	38	8	76.4 (7.4)		37	4	85.6 (6.7)	
Overweight	21	3	95.2 (4.6)		20	0	100	
Obese	15	4	85.6 (9.5)		14	1	90.0 (9.5)	
History of OCP use				0.44				0.36
No	20	4	83.5 (8.7)		19	2	88.1 (7.9)	
Yes	28	4	88.4 (6.3)		28	1	95.0 (4.9)	
Parity				0.75				0.16
Nulliparous	22	4	84.1 (8.5)		21	0	100	
Parous	67	13	83.4 (4.8)		63	6	87.6 (4.8)	
Menopausal status				0.37				0.07
Pre-menopausal	69	14	81.9 (5.0)		68	3	94.1 (3.3)	
Post-menopausal	25	8	73.5 (9.3)		21	3	78.8 (11.1)	
History of HRT use				0.16				**0.018**
No	53	13	79.8 (5.7)		52	4	90.5 (4.5)	
Yes	7	3	50.0 (20.4)		6	2	50.0 (25.0)	
History of breast cancer				0.13				0.46

Continued

Table 3 Continued

Variable	PFS				DSS			
	Patients, n	Events, n	5-year % (±SE)	P value	Patients, n	Events, n	5-year % (±SE)	P value
No	82	21	78.3 (4.8)		78	6	89.7 (4.0)	
Yes	9	0	100		8	0	100	
History of tamoxifen use				0.47				0.65
No	89	21	79.7 (4.6)		84	6	90.2 (3.8)	
Yes	3	0	100		3	0	100	
History of diabetes				0.54				0.83
No	89	21	79.9 (4.5)		84	6	90.5 (3.7)	
Yes	3	0	NR		3	0	NR	
BSO prior to diagnosis				0.21				
No	94	21	79.5 (4.5)		89	6	90.8 (3.6)	
Yes	1	1	100		0	NA		
LVSI				0.40				0.82
No	15	3	79.0 (10.8)		13	1	90.0 (9.5)	
Yes	59	16	78.1 (5.9)		57	5	88.0 (5.0)	
Lymph nodes sampled				0.64				0.91
No	52	11	81.0 (5.7)		48	3	91.5 (4.7)	
Yes	43	11	78.3 (6.8)		41	3	90.2 (5.4)	
Lymph node metastasis				0.86				0.14
No	38	10	79.2 (7.1)		36	2	92.9 (4.9)	
Yes	5	1	66.7 (27.2)		5	1	66.7 (27.2)	
Ovary or ovaries preserved				0.98				0.57
No	89	21	79.7 (4.6)		83	6	90.4 (3.8)	
Yes	6	1	83.3 (15.2)		6	0	100	

BMI, body mass index; BSO, bilateral salpingo-oophorectomy; DSS, disease-free survival; HRT, hormone replacement therapy; LVSI, lymphovascular space invasion; NA, not available; NR, not reached; OCP, oral contraceptive pills; PFS, progression-free survival; SE, standard error.

to draw firm conclusions.[9] Prior large-population database studies have reported no overall survival or disease-specific survival benefit with lymphadenectomy.[10 11] In our series, there was no progression-free or disease-specific survival benefit for patients who either underwent lymph node sampling or had metastatic disease to the lymph nodes. Routine systematic lymphadenectomy in patients without obvious adenopathy should not be performed given the low rate of occult lymph node metastasis and lack of evidence

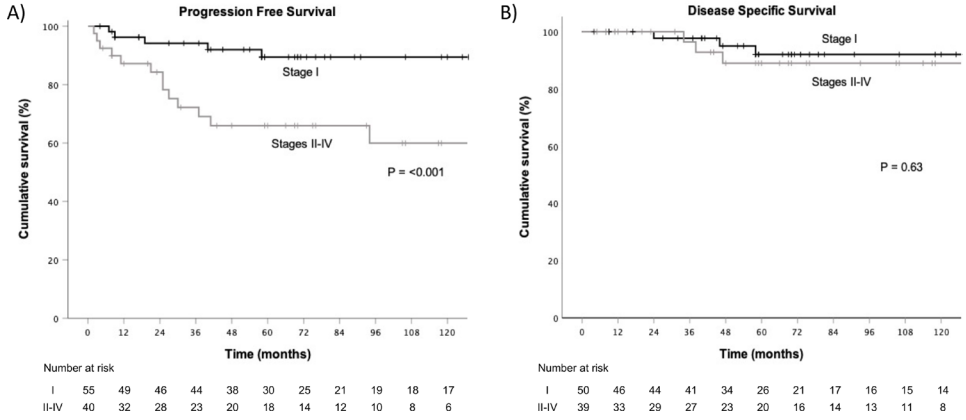

Figure 1 Kaplan-Meier curve estimates with respective number-at-risk charts for (A) progression-free survival and (B) disease-specific survival by stage I versus collective stage II–IV disease.

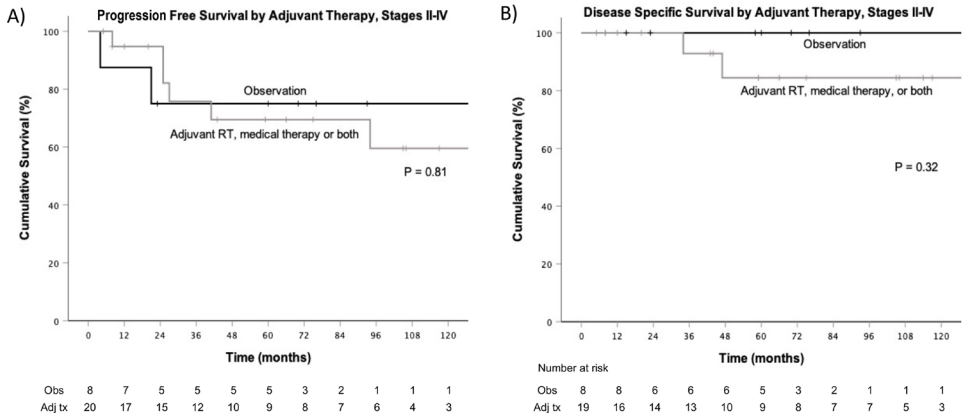

Figure 2 Kaplan-Meier curve estimates with respective number-at-risk charts for (A) progression-free survival and (B) disease-specific survival for patients with stage II-IV disease who had post-operative observation versus adjuvant radiation therapy (RT), medical therapy, or both.

supporting a survival benefit. Selective lymph node resection is a consideration for patients with clinically suspicious lymphadenopathy in order to achieve a complete resection of all tumor.

Stage was the only variable with a statistically significant relationship to progression-free survival. Patients with stage I disease lived longer without recurrence than those with stage II–IV disease. The association did not hold true for disease-specific survival, probably owing to the indolent nature of low-grade endometrial stromal sarcoma regardless of stage at presentation. These findings are consistent with prior studies.[11 12] Our results also uphold the overall 2018 FIGO staging system. However, a tumor size cut-off value of 5 cm in our stage I cases was not prognostic of outcome and brings into question the usefulness of FIGO substaging by tumor size.

The progression-free survival benefits observed for uterine tumor size ≤5 cm and for patients without residual tumor after resection were probably confounded by including all stages in the initial analyses. When selecting for stage I and stage II–IV tumors in the analysis of uterine tumor size and residual tumor on progression-free survival, respectively, the significance did not remain. The 5 cm threshold for substaging uterine-confined tumors was applied when a new staging system for endometrial stromal sarcoma and uterine leiomyosarcoma took effect in 2009 to prevent inappropriate upstaging from the older American Joint Committee on Cancer staging system,[2] although there is mixed evidence to support the application of this size cut-off point to endometrial stromal sarcoma.[13 14] Our results challenge the 5 cm threshold and thus the applicability of FIGO IA and IB substages to survival for stage I low-grade endometrial stromal sarcoma. The significant disease-specific survival benefit of no hormone replacement therapy use prior to the diagnosis of low-grade endometrial stromal sarcoma in our study may not be a reliable finding given the small cohort size and lack of progression-free survival benefit. Use of hormone replacement therapy has not been associated with a risk of developing low-grade endometrial stromal sarcoma and should be used in post-menopausal women as deemed appropriate. However, most data discourage the use of hormone replacement therapy in patients once they have been diagnosed and treated for low-grade endometrial stromal sarcoma.[15]

The most recent National Comprehensive Cancer Network (NCCN) guidelines mention that bilateral salpingo-oophorectomy is preferred in women with stage I low-grade endometrial stromal sarcoma, which suggests it is still debatable.[4] The question of ovarian preservation does arise with the many women who are premenopausal at the time of their diagnosis. Prior large-population database studies demonstrated that ovarian preservation was not a significant prognostic factor for survival, noting that ovary-sparing techniques may be considered in younger patients with stage I–II disease.[10 11] A recent systematic review and meta-analysis found a significantly increased tumor recurrence rate in the ovarian preservation group, but there was no difference in death rate.[16] Our results showed no difference in either progression-free or disease-specific survival for patients with at least one ovary preserved; however, there were only six patients with follow-up data who did not undergo initial bilateral salpingo-oophorectomy as part of their treatment. Of these patients, with a median follow-up of 47 months (range 8–118 months), there was only one recurrence in a patient initially diagnosed with a stage IIA low-grade endometrial stromal sarcoma at 19 years of age. We cannot draw firm conclusions with these small numbers, but along with evidence from prior larger studies, it seems reasonable to at least consider ovarian preservation in well-informed patients with stage I low-grade endometrial stromal sarcoma.

The NCCN recommends post-operative estrogen blockade for stage II–IV low-grade endometrial stromal sarcoma and notes that adjuvant external-beam radiation therapy may be added for stage II–IVA disease and palliative external-beam radiation therapy for stage IVB disease.[4] The aforementioned meta-analysis also analyzed pooled effects of adjuvant hormonal therapy from prior retrospective studies. The results favored hormone therapy; however, the authors acknowledged that non-hormonal confounding factors might have been responsible for the findings.[16] Data regarding the use of adjuvant radiation therapy for low-grade endometrial stromal sarcoma is primarily limited to retrospective studies, with mixed results,[17 18] or population database studies that do not distinguish low-grade from high-grade endometrial stromal sarcoma or even other uterine sarcomas.[19 20] Our analysis of the impact of adjuvant therapy, grouped as any adjuvant medical or radiation therapy, on progression-free and disease-specific survival did not suggest a benefit in either stage I or stage II–IV disease. We emphasize that these analyses were applied only to patients with

no residual disease after primary resection and that the number of patients available for follow-up in these cohorts was small. Patients with residual disease may benefit from post-operative estrogen blockade,[21] but our study did not show benefit of post-operative medical therapy over observation for those with residual disease. The number of patients was small, however, and most received treatment.

Strengths and Weaknesses

The strengths of our study include its large cohort from a single institution regarding a rare cancer. Population database studies capture large sample sizes, but their results are confounded by the inability to separate low-grade endometrial stromal sarcoma from high-grade endometrial stromal sarcoma. Our median follow-up period was nearly 6 years, with a maximum of 28 years, allowing for the assessment of long-term outcomes and analyses of multiple variables on survival. The limitations of our study include the inherent selection bias of retrospective studies. Comparing outcomes within a cohort spanning 40 years is also a limitation; however, low-grade endometrial stromal sarcoma interventions have not changed significantly over these 40 years. Another limitation is that the pathologic criteria for low-grade endometrial stromal sarcoma have changed over the 40-year study period; we hope expert review using modern criteria have mitigated this limitation.

Implications for Practice and Future Research

Future large-scale analyses via systematic reviews with meta-analyses may be necessary to best evaluate questions regarding low-grade endometrial stromal sarcoma, as the rarity of the disease and indolent disease course make prospective studies very challenging. Correlation of disease outcomes with molecular diagnostics may contribute to our understanding of disease prognosis and treatment options.

CONCLUSIONS

In our study, the rate of occult lymph node metastasis based on grossly normal lymph nodes and no extra-uterine disease was 3.4%. This low rate, as well as the lack of associated survival benefit, suggests that lymph node dissection in patients with low-grade endometrial stromal sarcoma should be selective and reserved for those with clinically suspicious lymphadenopathy. Furthermore, post-operative therapy did not improve survival, and ovary retention was not associated with recurrence. Our findings may help practitioners in the clinical management of low-grade endometrial stromal sarcoma, a disease in which there is still much controversy surrounding the benefit of lymphadenectomy, ovarian removal in early-stage tumors, and adjuvant therapy for completely resected disease.

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