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Original Article

Adjuvant hormone therapy and overall survival among low-grade and apparent early-stage endometrial stromal sarcoma patients

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: Surgery is the mainstay of treatment for low-grade endometrial stromal sarcoma (LG-ESS). While adjuvant hormone therapy is recommended for patients with advanced/recurrent disease, no consensus regarding its use among early-stage patients exists. We aimed to identify correlates of adjuvant hormone therapy use and associations of adjuvant hormone therapy and overall survival (OS) in stage I LG-ESS patients.
Methods: Retrospective cohort study of patients with stage I LG-ESS who underwent hysterectomy from 2004-2019 using data from the National Cancer Database. Categorical data were compared using χ^2 tests. Kaplan-Meier estimates and log-rank tests were used to compare OS according to adjuvant hormone use. Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between adjuvant hormone use and OS were estimated using Cox proportional hazards regression.
Results: Of 2,386 patients included, 20.2% were treated with adjuvant hormonal therapy. Use of hormone therapy increased over time, with rates approximately doubling from 2004 to 2019 (12.6% to 24.6%). Age, tumor size, lymphovascular space invasion and adjuvant radiation were associated with adjuvant hormone therapy use. There was no association between adjuvant hormone therapy and OS (log-rank p=0.73; HR=1.05; 95% CI=0.76–1.46) for patients with LG-ESS.
Conclusion: Use of adjuvant hormone therapy for stage I LG-ESS has increased over time though is not associated with OS in this cohort of patients. Additional evaluation is needed to understand the impact of adjuvant hormone therapy on recurrence rates, progression rates, and quality of life to fully understand its value.

Keywords: Endometrial Stromal Sarcoma; Adjuvant Treatment

Synopsis

Low-grade endometrial stromal sarcoma (LG-ESS) has near universal immunoreactivity for estrogen and/or progesterone receptors. Adjuvant hormonal therapy for patients with early-stage LG-ESS increased over the study period. Adjuvant hormone therapy is not associated with overall survival in patients with early-stage LG-ESS.

Author Contributions
Conceptualization: B.K.; Formal analysis: M.C.E., F.A.S.; Methodology: B.K., M.C.E., F.A.S.; Resources: F.A.S.; Supervision: B.K.; Writing - original draft: B.K.; Writing - review & editing: B.K., M.C.E., B.M., F.A.S.

INTRODUCTION

Endometrial stromal sarcomas (ESSs) account for less than 1% of uterine cancers and up to 20% of uterine sarcomas [1,2]. Low-grade ESS (LG-ESS) is characterized by cytologically bland spindle cells resembling proliferative endometrial stroma with finger-like myoinvasion with or without lymphovascular space invasion (LVSI) [3]. LG-ESS typically occurs between 40 and 55 years old and most patients are diagnosed with early-stage disease [4]. While the 5-year overall survival (OS) rate exceeds 80%, there is a high rate of recurrence (upwards of 40%) and 15-20% of patients will die of their disease [1,3,5-9]. Recurrence is often delayed, occurring a median of six to eight years after diagnosis [10,11]. This delayed progression and relative rarity of LG-ESS presents challenges for prospective studies of treatment efficacy.

Surgical management with total hysterectomy and bilateral salpingo-oophorectomy (BSO) is the cornerstone of treatment for this disease [2,4,12]. Uniform consensus on the role of adjuvant therapy following surgery for LG-ESS is lacking. LG-ESS tumors have a very low mitotic index and thus are poorly responsive to chemotherapy. Further, radiation has not demonstrated a survival benefit [13]. LG-ESS has near universal expression of estrogen receptors (ERs) and progesterone receptors (PRs) making hormonal therapy (including progestins, aromatase inhibitors, antiestrogens, and GnRH agonists) an attractive target [14].

Treatment recommendations for LG-ESS currently reflect associations identified from case reports and small, single institution retrospective cohorts [13,15-22]. Based on these data, the National Comprehensive Cancer Network (NCCN) recommends consideration of anti-estrogen hormone therapy with or without radiation following surgical resection for patients with advanced disease. Currently, observation alone is recommended for early-stage LG-ESS patients without high-risk features, for example, morcellation at the time of hysterectomy [7]. Retrospective studies, however, do suggest improved recurrence-free survival with use of adjuvant hormone therapy in early-stage disease [9,23]. To further clarify the role of adjuvant hormone therapy among stage I LG-ESS patients, we examined factors associated with adjuvant hormone therapy use and the impact of adjuvant hormone therapy on survival using a large cancer registry.

MATERIALS AND METHODS

1. Data source

Data were obtained from the hospital-based National Cancer Database (NCDB) [24], a cancer registry capturing 70% of cancers diagnosed in the United States. Abstracted data include sociodemographic characteristics, tumor characteristics, treatment facility attributes, treatment, and survival outcomes abstracted from patient medical records by Certified Tumor Registrars [25]. Data submitted to NCDB undergo rigorous quality checks according to American College of Surgeons standards. This study was exempt from the Ohio State Institutional Review Board, and we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [26].

2. Study population

We defined a retrospective cohort study of patients diagnosed with ESS using International Classification of Disease for Oncology, Third Edition (ICD-O-3) morphology codes 8930 (ESS) and 8931 (LG-ESS) between 2004 and 2019 using data from the NCDB (n=5,988)

[24,25]. As described by Seagle et al. [27], we excluded patients with histology code 8930 with grade III/IV (n=1,856) or unknown grade (n=961) and patients with histology code 8931 with grade III/IV (n=26) to identify our target sample of patients with LG-ESS (n=3,145 retained). We further excluded patients for the following reasons: surgical procedures not classified as subtotal or total abdominal hysterectomy +/- BSO (n=337); systemic therapy before surgery (n=17); unknown systemic therapy/surgery sequence (n=52); radiation therapy before surgery (n=3); unknown radiation therapy/surgery sequence (n=60); unknown or positive regional lymph nodes (n=121); metastasis found at diagnosis (n=155); unknown adjuvant hormone therapy treatment (n=15); and follow up time of 0 months or unknown follow up time (n=1) resulting in a sample size of 2,386 patients.

3. Primary outcome

OS was calculated as the time from the date of diagnosis to the date of death. Among those alive at the end of follow-up, the date of last contact was used as the censoring time.

4. Covariates

Patient demographics included age at diagnosis (<50, 50–69, ≥70), race/ethnicity (Non-Hispanic White, hereafter referred to as White, Non-Hispanic Black, hereafter referred to as Black, Hispanic ethnicity of any race, and Non-Hispanic Other, hereafter referred to as Other), Charlson-Deyo comorbidity score (0, 1, or ≥2), type of health insurance (none, private, Medicaid, Medicare, other government), area-level income (<$46,277, $46,277–$57,856, $57,857–$74,062, ≥74,063), area-level educational attainment (measure of the number of adults who did not graduate from high school; ≥15.3%, 9.1%–15.2%, 5%–9%, <5%). Area-level income was estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from the 2020 American Community Survey data, spanning years 2016–2020 and adjusted for 2020 inflation. Household income was categorized as quartiles based on equally proportioned income ranges among all US zip codes. Area-level education was estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from the 2020 American Community Survey data, spanning years 2016–2020. This item provides a measure of the number of adults aged 25 or older in the patient's zip code who did not graduate from high school and is categorized as equally proportioned quartiles among all US zip codes. Facility characteristics included location (Northeast, Midwest, Mountain, Pacific, South), and type (community cancer, comprehensive community cancer, academic/research, integrated network cancer).

Tumor characteristics included LVSI (no vs. yes, available starting in 2010) and tumor size (<5 cm, ≥5 cm). Surgical approach (available starting in 2010) was classified as robotic assisted laparoscopy (RAL), laparotomy, or laparoscopic. Surgical procedure was categorized as subtotal hysterectomy ± BSO or total abdominal hysterectomy ± BSO. Treatment coding in the NCDB is limited to the first course of treatment; we classified adjuvant hormone, radiation, and chemotherapy as no vs. yes. Unknown values were included as separate categories.

5. Statistical analysis

Distributions of patient, facility, tumor, and treatment characteristics according to adjuvant hormone treatment were compared using χ^2 tests. Adjuvant hormone therapy use prevalence was plotted according to year of diagnosis. Kaplan-Meier estimates and log-rank tests were used to compare OS according to adjuvant hormone use. Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between adjuvant hormone use and OS were

estimated using univariable and multivariable-adjusted Cox proportional hazards regression adjusted for age (continuous, reported per 5-year increment), tumor size (<5 cm, ≥5 cm), surgical approach (RAL, laparotomy, and laparoscopic), LVSI (no, yes), chemotherapy (no, yes), radiation (no, yes), and year of diagnosis. Adjustment factors were selected *a priori* based on potential prognostic factors identified in the literature and although the prognostic significance of radiation is controversial, we included this as a covariate to provide additional data [4,28]. We assessed the proportional hazards assumption by examining plots of the Schoenfeld residuals vs. log follow-up time for hormone use and noted no significant violations. All analyses were performed in SAS version 9.4. All p-values were two-sided.

RESULTS

Among 2,386 stage I low-grade ESS patients, 20.2% were treated with adjuvant hormone therapy. **Fig. 1** demonstrates rates of adjuvant hormone therapy use annually over the study period. Overall, use of hormone therapy increased over time with rates approximately doubling over the study period (12.6% to 24.6%). Compared to patients who did not receive adjuvant hormone therapy, patients who received adjuvant hormone therapy were more likely to be diagnosed at ages 50–69, reside in zip codes with a higher proportion of individuals with a high school diploma, be diagnosed after 2013, have larger tumors (≥5 cm), and have LVSI (**Table 1**). Adjuvant hormone therapy use was more common among those treated with radiation, however less common in those who received chemotherapy. Race, comorbid conditions, insurance status, income, and type of hysterectomy (total vs. subtotal) did not differ between groups. There was no association between ovarian retention versus removal and adjuvant hormone therapy use.

Median follow-up in this sample was 77 months (range 0.03–210.2 months). Over the follow-up period, 9.1% of those treated with adjuvant hormone therapy died compared to 10.1% of those not treated with adjuvant hormone therapy. Adjuvant hormone therapy was not associated with OS in univariable (log-rank p=0.73; HR=1.05; 95% CI=0.76–1.46; **Fig. 2**) or multivariable-adjusted models (**Table 2**; HR=1.05; 95% CI=0.73–1.50). Other factors associated with worse OS in this patient sample included older age at diagnosis (HR per 5-year increment=1.49; 95%

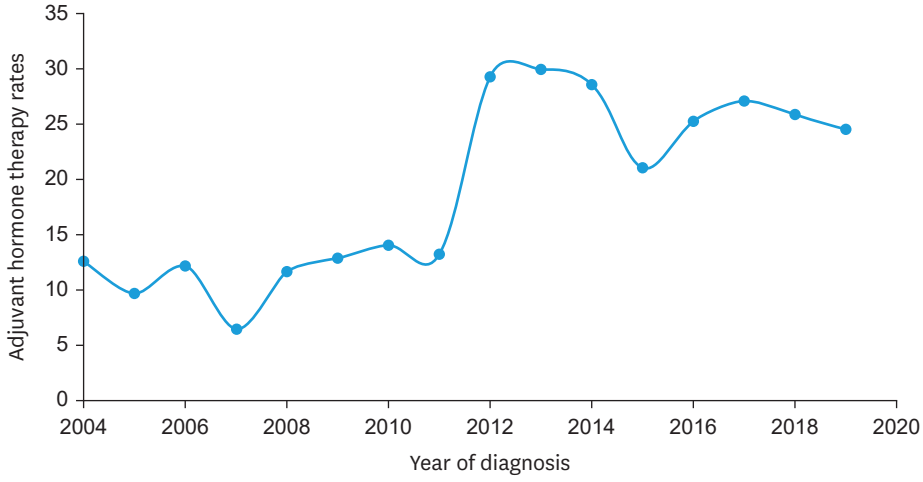

Fig. 1. Adjuvant hormone therapy use over time in the overall study population.
Fig. 1 shows increases in adjuvant hormone therapy use over time.

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Table 1. Characteristics of stage I low-grade endometrial stromal sarcoma patients overall and by adjuvant hormone therapy use, National Cancer Database 2004–2019

Characteristics	Overall (n=2,386)	No adjuvant hormone therapy (n=1,904)	Adjuvant hormone therapy (n=482)	p-value
Age (yr)				0.01
<50	1,291 (54.1)	1,058 (55.6)	233 (48.3)	
50–69	916 (38.4)	703 (36.9)	213 (44.2)	
≥70	179 (7.5)	143 (7.5)	36 (7.5)	
Mean ± SD	50.4±11.5	50.4±11.5	50.7±11.5	0.10
Race				0.59
White	1,626 (68.2)	1,293 (67.9)	333 (69.1)	
Black	269 (11.3)	213 (11.2)	56 (11.6)	
Hispanic	248 (10.4)	203 (10.7)	45 (9.3)	
Other	140 (5.9)	108 (5.7)	32 (6.6)	
Unknown	103 (4.3)	87 (4.6)	16 (3.3)	
Charlson-Deyo score				0.17
0	2,035 (85.3)	1,637 (86.0)	398 (82.6)	
1	276 (11.6)	210 (11.0)	66 (13.7)	
≥2	75 (3.1)	57 (3.0)	18 (3.7)	
Insurance status				0.29
No insurance	129 (5.4)	100 (5.3)	29 (6.0)	
Private insurance	1,659 (69.5)	1,322 (69.4)	337 (69.9)	
Medicaid	204 (8.6)	160 (8.4)	44 (9.1)	
Medicare	327 (13.7)	261 (13.7)	66 (13.7)	
Other government	31 (1.3)	29 (1.5)	2 (0.4)	
Unknown	36 (1.5)	32 (1.7)	4 (0.8)	
Area-level annual income ($)				0.19
Quartile 1: <46,277	324 (13.6)	260 (13.7)	64 (13.3)	
Quartile 2: 46,277 to 57,856	439 (18.4)	353 (18.5)	86 (17.8)	
Quartile 3: 57,857 to 74,062	485 (20.3)	395 (20.8)	90 (18.7)	
Quartile 4: ≥74,063	848 (35.5)	680 (35.7)	168 (34.9)	
Unknown	290 (12.2)	216 (11.3)	74 (15.4)	
Area-level education, % of residents without high school diploma				0.02
Quartile 1: <5.0	465 (19.5)	371 (19.5)	94 (19.5)	
Quartile 2: 5.0 to 9.0	588 (24.6)	459 (24.1)	129 (26.8)	
Quartile 3: 9.1 to 15.2	634 (26.6)	529 (27.8)	105 (21.8)	
Quartile 4: ≥15.3	412 (17.3)	332 (17.4)	80 (16.6)	
Unknown	287 (12.0)	213 (11.2)	74 (15.4)	
Facility location				0.0005
Northeast	439 (18.4)	325 (17.1)	114 (23.7)	
South	730 (30.6)	616 (32.4)	114 (23.7)	
Midwest	547 (22.9)	423 (22.2)	124 (25.7)	
Mountain	105 (4.4)	89 (4.7)	16 (3.3)	
Pacific	268 (11.2)	215 (11.3)	53 (11.0)	
Unknown	297 (12.5)	236 (12.4)	61 (12.7)	
Facility type				0.001
Community cancer program	98 (4.1)	88 (4.6)	10 (2.1)	
Comprehensive community cancer program	769 (32.2)	637 (33.5)	132 (27.4)	
Academic/Research program	824 (34.5)	624 (32.8)	200 (41.5)	
Integrated network cancer program	398 (16.7)	319 (16.8)	79 (16.4)	
Unknown	297 (12.5)	236 (12.4)	61 (12.7)	
Year of diagnosis				<0.0001
2004–2006	336 (14.1)	297 (15.6)	39 (8.1)	
2007–2009	394 (16.5)	353 (18.5)	41 (8.5)	
2010–2012	466 (19.5)	375 (19.7)	91 (18.9)	
2013–2015	487 (20.4)	357 (18.8)	130 (27.0)	
2016–2019	703 (29.5)	522 (27.4)	181 (37.6)	
Tumor size				<0.0001
<5 cm	758 (31.8)	649 (34.1)	109 (22.6)	
≥5 cm	1,079 (45.2)	805 (42.3)	274 (56.9)	
Unknown	549 (23.0)	450 (23.6)	99 (20.5)	

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Table 1. (Continued) Characteristics of stage I low-grade endometrial stromal sarcoma patients overall and by adjuvant hormone therapy use, National Cancer Database 2004–2019

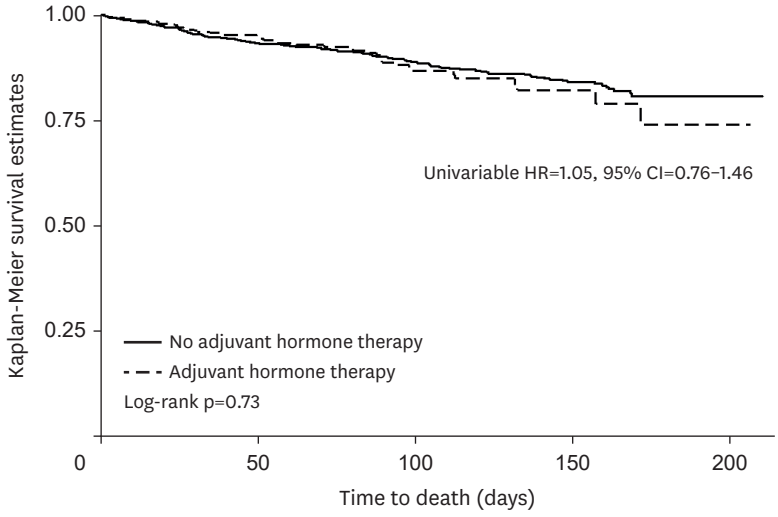
Characteristics	Overall (n=2,386)	No adjuvant hormone therapy (n=1,904)	Adjuvant hormone therapy (n=482)	p-value
LVSI*				<0.0001
No	672 (28.2)	548 (28.8)	124 (25.7)	
Yes	670 (28.1)	447 (23.5)	223 (46.3)	
Unknown	1,044 (43.8)	909 (47.7)	135 (28.0)	
Surgery				0.91
Subtotal hysterectomy ± BSO	141 (5.9)	112 (5.9)	29 (6.0)	
TAH ± BSO	2,245 (94.1)	1,792 (94.1)	453 (94.0)	
Bilateral salpingo-oophorectomy				0.09
No	372 (15.6)	312 (16.4)	60 (12.5)	
Yes	1,954 (81.9)	1,543 (81.0)	411 (85.3)	
Unknown	60 (2.5)	49 (2.6)	11 (2.3)	
Surgical approach*				0.02
Robotic-assisted	491 (20.6)	383 (20.1)	108 (22.4)	
Laparotomy	663 (27.8)	508 (26.7)	155 (32.2)	
Laparoscopic	367 (15.4)	299 (15.7)	68 (14.1)	
Unknown	865 (36.3)	714 (37.5)	151 (31.3)	
Chemotherapy				0.02
No	2,316 (97.1)	1,839 (96.6)	477 (99.0)	
Yes	56 (2.4)	53 (2.8)	3 (0.6)	
Unknown	14 (0.6)	12 (0.6)	2 (0.4)	
Radiation				0.04
No	2,153 (90.2)	1,732 (91.0)	421 (87.3)	
Yes	231 (9.7)	170 (8.9)	61 (12.7)	
Unknown	2 (0.1)	2 (0.1)	0 (0.0)	

BSO, bilateral salpingo-oophorectomy; TAH, total abdominal hysterectomy.
*Variable not available for cases prior to 2010. Unknown value contains all cases from 2004–2009.

CI=1.41–1.56), larger tumor size (≥5 cm vs. <5 cm; HR=1.45; 95% CI=1.03–2.04), presence of LVSI (HR=1.48; 95% CI=0.98–2.21), and adjuvant chemotherapy (HR=5.37; 95% CI=3.43–8.40). Patients with a laparoscopic surgical approach had improved OS (laparoscopic vs. robotic assisted HR=0.52; 95% CI=0.27–0.99).

In this retrospective cohort of stage I LG-ESS patients, approximately one in five patients were treated with adjuvant hormone therapy, with the proportion rising over the duration of the study. Among those diagnosed from 2004–2006, 11.6% received adjuvant hormone therapy compared with 25.7% of patients diagnosed from 2016–2019. Unsurprisingly, patient age, tumor size, and presence of LVSI (known factors associated with increased risk of recurrence) were associated with adjuvant hormone therapy. While a trend of increasing use of adjuvant hormone therapy over time was identified, potentially reflecting a perception that hormone treatment may prevent recurrence, we did not detect univariable or multivariable-adjusted associations between adjuvant hormone therapy and OS.

Most LG-ESS tumors are immunoreactive for ERs and/or PRs. The NCCN currently recommends adjuvant hormone therapy for patients with advanced (stage II or greater) or recurrent LG-ESS [3]. Options for hormonal therapy include aromatase inhibitors, progestins, GnRH analogues or ER antagonists though aromatase inhibitors are preferred according to national guidelines [4]. For patients with advanced or recurrent disease not amenable to surgery, objective response rates to hormonal therapy vary widely in the literature, however the rate of clinical benefit is universally high. In a single institution retrospective cohort of 47 patients diagnosed with recurrent LG-ESS between 1995 and 2006; 17% of those who received adjuvant hormone therapy had a complete response, 3% had a



No. at risk									
No adjuvant hormone therapy	1,904	(111)	1,291	(46)	724	(28)	288	(7)	14
Adjuvant hormone therapy	482	(22)	303	(16)	125	(4)	37	(2)	1

Fig. 2. Overall survival according to adjuvant hormone therapy use.
Fig. 2 shows no significant difference in overall survival among stage I low-grade endometrial stromal sarcoma patients according to adjuvant hormone therapy.
CI, confidence interval; HR, hazard ratio.

partial response, and 53% had stable disease whereas patients who received chemotherapy or radiation (with no hormonal therapy) had no documented responses [11]. Thanopoulou et al. [29] evaluated 13 patients with metastatic ESS in which first-line endocrine therapy achieved an objective response rate of 46.2% and a clinical benefit rate of 92.4%. Though second-line hormonal therapy did not yield an objective response in this cohort, all patients (10/10) had stable disease representing 100% clinical benefit.

Only two prospective studies have evaluated endocrine therapy in patients with LG-ESS and these studies were limited to patients with advanced or recurrent disease. Ramondetta et al. [30] performed a phase II trial of mifepristone in advanced or recurrent PR positive endometrioid adenocarcinoma (n=10) or LG-ESS (n=2). Most patients received chemotherapy and radiotherapy prior to enrollment. In this study, 75% of patients progressed while 25% had stable disease (including 1 of 2 patients with LG-ESS) [30]. In the PARAGON basket trial of anastrozole in ER + and/or PR + tumors, which included 15 postmenopausal LG-ESS patients with no prior anti-cancer endocrine therapy and measurable disease, the objective response rate was 26%, including one complete response (6.7%) and three partial responses (20%), with an additional 7 patients having stable disease (46.7%) [31]. Overall, the promising benefits of endocrine therapy in advanced stage LG-ESS prompted our investigation of its role in early-stage disease.

While observation is typically recommended for early-stage disease, late recurrence even among early-stage disease is high, prompting an assessment of adjuvant hormone therapy in the setting of early-stage disease. Prior studies are limited, but overall suggest a benefit. Chu et al. published a case series of 17 patients with stage I LG-ESS. Of these, 10 patients received progestin therapy, 3 had no adjuvant therapy, and 4 had estrogen containing hormone replacement therapy. Two of the 10 patients treated with adjuvant progestin therapy

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Table 2. Multivariable adjusted HRs and 95% CIs for associations of adjuvant hormone use, clinical factors, and overall survival

Variables	Deaths, No. (%)*	HR (95% CI)†	p-value
Hormone therapy use			0.80
No	192/1,904 (10.1)	1.00	
Yes	44/482 (9.1)	1.05 (0.73–1.50)	
Age	-	1.49 (1.41–1.57)	<0.0001
Year of diagnosis			0.99
2004–2006	50/336 (14.9)	1.00	
2007–2009	61/394 (15.5)	1.00 (0.68–1.47)	
2010–2012	51/466 (10.9)	0.91 (0.42–1.99)	
2013–2015	43/487 (8.8)	1.00 (0.45–2.23)	
2016–2019	31/703 (4.4)	0.90 (0.38–2.08)	
Tumor size			0.07
<5 cm	49/758 (6.5)	1.00	
≥5 cm	132/1,079 (12.2)	1.45 (1.03–2.04)	
Unknown	55/549 (10.0)	1.15 (0.78–1.71)	
LVSI‡			0.15
No	42/672 (6.3)	1.00	
Yes	59/670 (8.8)	1.48 (0.98–2.21)	
Unknown	135/1,044 (12.9)	1.12 (0.67–1.88)	
Surgical approach‡			0.12
Robotic assisted	31/491 (6.3)	1.00	
Laparotomy	69/663 (10.4)	1.07 (0.69–1.66)	
Laparoscopic	13/367 (3.5)	0.52 (0.27–0.99)	
Unknown	123/865 (14.2)	1.08 (0.54–2.15)	
Chemotherapy			<0.0001
No	210/2,316 (9.1)	1.00	
Yes	24/56 (42.9)	5.37 (3.43–8.40)	
Unknown	2/14 (14.3)	0.40 (0.10–1.64)	
Radiation			0.01
No	193/2,153 (9.0)	1.00	
Yes	42/231 (18.2)	1.32 (0.93–1.88)	
Unknown	1/2 (50.0)	14.68 (1.98–108.78)	

CI, confidence interval; HR, hazard ratio; LVSI, lymphovascular space invasion.
*Row percentages.
†HRs and 95% CIs adjusted for hormone use, age, year of diagnosis, tumor size, LVSI, surgical approach, chemotherapy, and radiation.
‡Variables not available for cases prior to 2010. Unknown value contains all cases from 2004–2009.

recurred (20%) compared with 5 of 7 (71%) who received no adjuvant therapy or estrogen containing hormone replacement therapy [23]. Malouf et al. [32] evaluated the role of adjuvant therapy in a retrospective cohort of 54 stage I-II ESS patients, of whom 10 received adjuvant hormone therapy and 13 received radiation therapy. None of the patients who received adjuvant therapy recurred (10 patients treated with hormone therapy and 13 with radiation) whereas 42% (13/31) of patients who had not received adjuvant therapy experienced a relapse. In another retrospective review of 39 patients who underwent hysterectomy for low-grade ESS, 30 had stage I disease. In this subset, 70% (7/10) of patients who received no hormonal therapy recurred compared with 14.3% (1/7) of those receiving an aromatase inhibitor and 7.7% (1/13) receiving progestins (p=0.003) [9]. Overall, studies evaluating the impact of adjuvant hormone therapy on recurrence for this disease are limited by small sample sizes given the rarity and indolent nature of this tumor.

The current study is the largest to examine the impact of adjuvant hormone therapy on survival for patients with early-stage LG-ESS. The current study is limited by the challenges known to large cancer registry studies, including a lack of treatment specificity, notably hormonal agents, dose, and duration of treatment. Additionally, potential confounders such

as body mass index (which may influence endogenous estrogen production via aromatase) are missing and data regarding the potential side effects or toxicities of adjuvant hormone therapy are not available. Given the concern for late recurrences, the absence of disease recurrence and cause-specific death are key limitations.

While this study failed to demonstrate an OS benefit with use of adjuvant hormone therapy for uterine confined LG-ESS, evaluation of the impact of adjuvant hormone therapy on late recurrences and quality of life remains important. While many recurrences may be salvaged with hormonal therapy, radiation therapy or surgical resection, the emotional, physical, and financial impact of recurrent disease can take a great toll on patients and families. Thus, despite the absence of an OS effect, future studies related to upfront adjuvant hormone therapy for recurrence prevention are needed as this may be of great benefit to patients.

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