Submitted: 01 November, 2022 Accepted: 16 March, 2023 Published: 15 April, 2023 DOI:10.22514/ejgo.2023.019

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Treatment patterns for leiomyosarcomas, endometrial stromal sarcomas and adenosarcomas: a national cancer database study

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Abstract

Uterine sarcomas are a rare, heterogenous, group of cancers with limited data on optimal adjuvant treatment. We examined patterns of care for leiomyosarcomas (LMS), endometrial stromal sarcomas (ESS), adenosarcomas (AS), and mixed uterine sarcomas and assessed the utilization of adjuvant therapy for each histology. The National Cancer Database (NCDB) was queried for patients with non-metastatic uterine sarcoma diagnosed between 2004 and 2018 treated with surgery. Uterine carcinosarcomas were excluded. Adjuvant patterns of care and temporal treatment trends are evaluated, stratified by histology. Multivariable logistic regression model was constructed to identify predictors of receipt of radiation adjuvant therapy. Among 12,806 patients, 88% received a total hysterectomy and bilateral salpingo-oophorectomy (TH+BSO) and 42% received lymph node sampling (LNS). Surgery alone was the most common treatment modality for all histology groups (59.0%). Surgery with chemotherapy was the second most common form of treatment for LMS (33.1%) and mixed type tumors (29.6%). Surgery with radiation was the second most common treatment for high-grade ESS (10.8%) and AS (11.8%). External beam radiation therapy (EBRT) was the most common type of adjuvant radiation therapy utilized. Adjuvant radiation therapy (RT) has declined in LMS, from 27% in 2004 to 3% in 2018. Adjuvant chemotherapy for all histology groups has increased in use from 10% in 2004 to 28% in 2018. For uterine sarcomas, TH+BSO without LNS was the main surgical modality. Adjuvant therapy for uterine sarcomas is not commonly used, however high risk features including stage II/III, high grade, and more extensive lymph node sampling appear to increase the likelihood of adjuvant RT. The utilization of adjuvant chemotherapy in uterine sarcomas has increased over time, while RT has been decreasing.

Keywords

Uterine sarcoma; Treatment; Radiation therapy; Chemotherapy; Surgery; Leiomyosarcoma; Endometrial stromal sarcoma; Adenosarcoma

1. Introduction

In 2022, an estimated 65,950 patients will be diagnosed with uterine corpus cancer and an estimated 12,550 will die from this disease [1]. Uterine sarcomas make up only 3–7% of uterine cancer but are more aggressive with the lowest rates of survival among uterine histologies [2, 3]. Studies of uterine sarcomas have included a histologically diverse subset of cancers, including: leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), adenosarcoma (AS), and carcinosarcoma (CS, now considered a subset of endometrial carcinoma) [4, 5]. In recent years, these differing histology groups have begun to be recognized as distinct entities requiring unique treatment approaches making it difficult to interpret prior studies which treated them as one entity [6, 7]. Due to the rarity of uterine sarcomas, treatment recommendations are largely drawn from retrospective studies and small phase I and II trials. Only one phase III trial for LMS, ESS and CS has been completed assessing the utilization of radiation therapy [8]. This phase III trial showed an improvement for local control (LC) with the addition of radiation therapy for CS but not for LMS. The patient population for ESS was too small to assess. Due to the lack of randomized data, decision-making regarding adjuvant treatment for uterine sarcomas can be challenging. We used the National Cancer Database (NCDB) to assess the utilization of adjuvant therapy, particularly radiation therapy, and elucidate adjuvant treatment trends over time.

2. Materials and methods

The National Cancer Database (NCDB) was queried for patients diagnosed with non-metastatic uterine sarcoma between 2004 and 2018 treated with upfront surgery including total hysterectomy (TH), TH plus bilateral salpingo-oophrectomy (BSO) and surgery not otherwise specified (NOS). Histology groups examined include leiomyosarcoma, low-grade ESS, high-grade ESS, adenosarcoma, and mixed histology. Patients who received neoadjuvant therapies and uterine carcinosarcoma histology were excluded. See Fig. 1 for a summary of inclusion and exclusion criteria. Available social, demographic, and clinical information was collected for all included patients (Table 1). The NCDB is a publicly available database established by the American Cancer Society and Commission on Cancer of the American College of Surgeons that captures 70% of all cancer diagnoses in the United States [9]. This study was exempt from institutional review board approval.

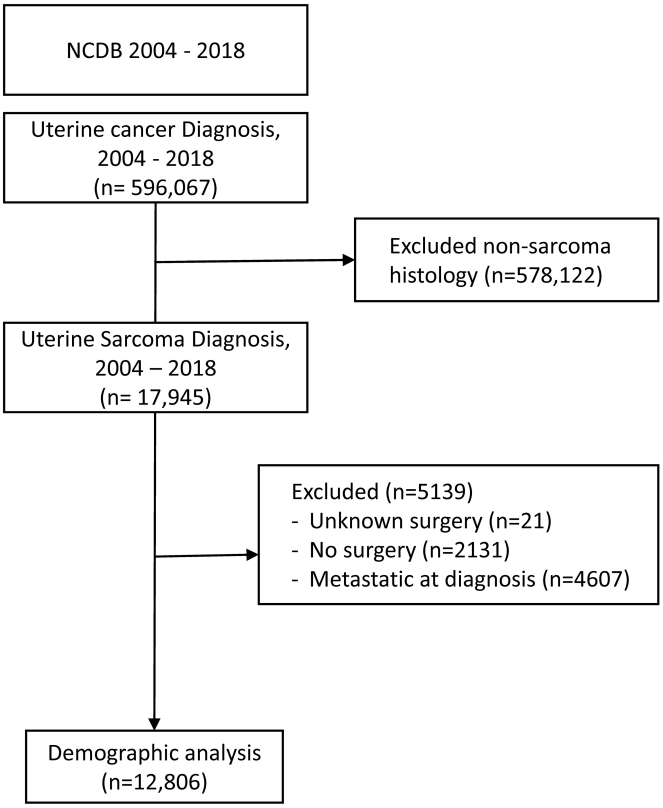

FIGURE 1. Patient inclusion and exclusion criteria. NCDB: National Cancer Database.

Patients were grouped by treatment administered as follows: surgery alone, surgery followed by radiation therapy, surgery followed by chemotherapy, or surgery followed by both radiation therapy and chemotherapy (concurrent or sequenced in any order). Radiation modality was grouped into EBRT, brachytherapy, and unknown. Chemotherapy usage was grouped as single agent, multiagent, or unknown type. Hormonal therapy usage was reported as a binary variable (yes/no). Receipt of immunotherapy was reported as a binary variable (yes/no) but has only been reported since 01 January 2013.

A forward stepwise logistic regression was used to identify potential predictors of receipt of radiotherapy out of the available clinical and patient variables. At each step, variables were selected for inclusion in the multivariable model based on the *p*-value from univariable logistic regression for receipt of radiotherapy with a *p*-value threshold of 0.2 used to limit the total number of variables in the final model. Multicollinearity within the multivariable model was not observed with variance inflation factors ranging from 1.0 to 1.06. Temporal trends in treatment are reported over the study period as an overall cohort and stratified by histology. All statistical analysis was conducted using STATA/IC-14 (version 14, StataCorp., College Station, TX, USA) [10].

3. Results

There were 12,806 patients in the NCDB who met our inclusion criteria: 61% LMS, 7% low-grade ESS, 5% high-grade ESS, 20% AS, and 7% mixed type (Table 1). For demographic information please refer to **Supplementary Table 1**. Of the patients queried, 88%, received a total hysterectomy and bilateral salpingo-oophorectomy (TH+BSO). Of the 41.6% of patients that had lymph nodes sampled, 13.1% had <7 lymph nodes and 28.1% with ≥ 7 lymph nodes sampled. The majority of tumors were stage I and 85% of tumors were larger than five centimeters in size.

The treatments rendered for different histology types are shown in Table 2. Surgery alone was most common for all histology groups (59.0%), followed by surgery with adjuvant chemotherapy (24.5%), surgery with adjuvant RT (10.6%), and surgery with adjuvant chemotherapy and RT was least common (5.8%). Surgery followed by chemotherapy was second most common for patients with LMS or mixed type tumors. Surgery with radiation was the second most common for patients with high-grade ESS and AS. Chemotherapy was rarely used for ESS. Hormone therapy was most frequently used in ESS for both the low and high grade tumors compared to the other subtypes at 17% and 22% respectively. If patients received adjuvant radiation therapy, EBRT was the most common type. When chemotherapy was provided, multiagent treatment was utilized. Adjuvant immunotherapy utilization was 0.34%.

Tumor size was not a significant predictor for radiation therapy when comparing smaller than 5 cm to larger than 5 cm for any histology group. Patients with a later year of diagnosis were less likely to receive radiation than those with an earlier diagnosis for LMS (odds ratio (OR) 0.86, $p < 0.001$) and ESS (OR 0.79, $p < 0.01$). Factors associated with radiation therapy utilization are described in Table 3.

Fig. 2 illustrates the trends in treatment over time for uterine sarcomas. Over time, there has been an increased use of chemotherapy while radiation therapy has been decreasing. Radiation therapy has rapidly declined in LMS, particularly after 2009. Surgery alone remains the most constant treatment choice compared to surgery with adjuvant therapies.

4. Discussion

Uterine sarcomas are a rare and histologically diverse cancer subset in which there is limited randomized evidence to guide treatment recommendations. This study utilized the

TABLE 1. Clinical information of queried uterine sarcoma patients.

	Leiomyosarcoma		Low grade ESS		High grade ESS		Adenosarcoma		Mixed		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade Group												
(0) Well-Differentiated	285	8	837	100	0	0	353	31	48	7	1523	22
(1) Moderately-Differentiated	474	14	0	0	606	98	282	25	23	3	1385	20
(2) Poorly-Differentiated	1652	47	0	0	14	2	279	25	195	27	2140	31
(3) Undifferentiated	1089	31	0	0	0	0	217	19	444	63	1750	26
Total	3500	100	837	100	620	100	1131	100	710	100	6798	100
Surgery												
TH	681	11	123	18	73	14	141	7	41	6	1059	10
TH+BSO	5402	88	531	79	425	84	1956	93	642	92	8956	88
Surgery, NOS	66	1	16	2	6	1	9	0	16	2	113	1
Total	6149	100	670	100	504	100	2106	100	699	100	10,128	100
Tumor Size												
Smaller than 5 cm	870	11	249	30	174	28	573	22	94	10	1960	15
Larger than 5 cm	6955	89	588	70	446	72	2006	78	851	90	10,846	85
Total	7825	100	837	100	620	100	2579	100	945	100	12,806	100
Path Stage Group												
I	2207	70	261	79	195	73	1031	90	168	63	3862	75
II	441	14	32	10	30	11	46	4	31	12	580	11
III	398	13	30	9	36	13	58	5	54	20	576	11
IV	114	4	9	3	6	2	14	1	15	6	158	3
Total	3160	100	332	100	267	100	1149	100	268	100	5176	100
LN Dissection												
No LN sampled	5064	65	498	59	378	61	1132	44	412	44	7484	58
<7 LN	1014	13	87	10	58	9	379	15	144	15	1682	13
≥7 LN	1747	22	252	30	184	30	1068	41	389	41	3640	28
Total	7825	100	837	100	620	100	2579	100	945	100	12,806	100
N	7825		837		620		2579		945		12,806	

TH: total hysterectomy; TH+BSO: total hysterectomy and bilateral salpingo-oophorectomy; NOS: not otherwise specified; LN: lymph node; ESS: endometrial stromal sarcomas.

TABLE 2. Adjuvant treatment patterns of care for uterine sarcomas.

	Leiomyosarcoma		Low-grade ESS		High-grade ESS		Adenosarcoma		Mixed		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Treatment Modality												
Surgery alone	3807	50.4	696	85.9	527	86.1	1848	73.7	429	47.5	7307	59.0
Surgery + RT	742	9.8	96	11.9	66	10.8	295	11.8	119	13.2	1318	10.6
Surgery + Chemo	2499	33.1	14	1.7	16	2.6	243	9.7	267	29.6	3039	24.5
Surgery + Chemo + RT	507	6.7	4	0.5	3	0.5	121	4.8	88	9.7	723	5.8
Total	7555		810		612		2507		903		12,387	
Radiation Modality												
EBRT	849	59.1	72	58.5	42	49.4	223	46.1	137	59.1	1323	56.1
Brachytherapy	377	26.3	28	22.8	26	30.6	183	37.8	64	27.6	678	28.7
Unknown	210	14.6	23	18.7	17	20.0	78	16.1	31	13.4	359	15.2
Total	1436		123		85		484		232		2360	
Chemotherapy												
Single agent	246	8.2	3	16.7	2	10.5	24	6.6	42	11.8	317	8.4
Multiagent	2616	87.0	14	77.8	14	73.7	323	88.7	291	82.0	3258	86.6
Unknown type	144	4.8	1	5.6	3	15.8	17	4.7	22	6.2	187	5.0
Total	3006		18		19		364		355		3762	
Hormone Therapy												
None	7685	98.2	698	83.4	482	77.7	2514	97.5	927	98.1	12,306	96.1
Yes	140	1.8	139	16.6	138	22.3	65	2.5	18	1.9	500	3.9
Total	7825		837		620		2579		945		12,806	

RT: radiation therapy; EBRT: external beam radiation; ESS: endometrial stromal sarcomas.

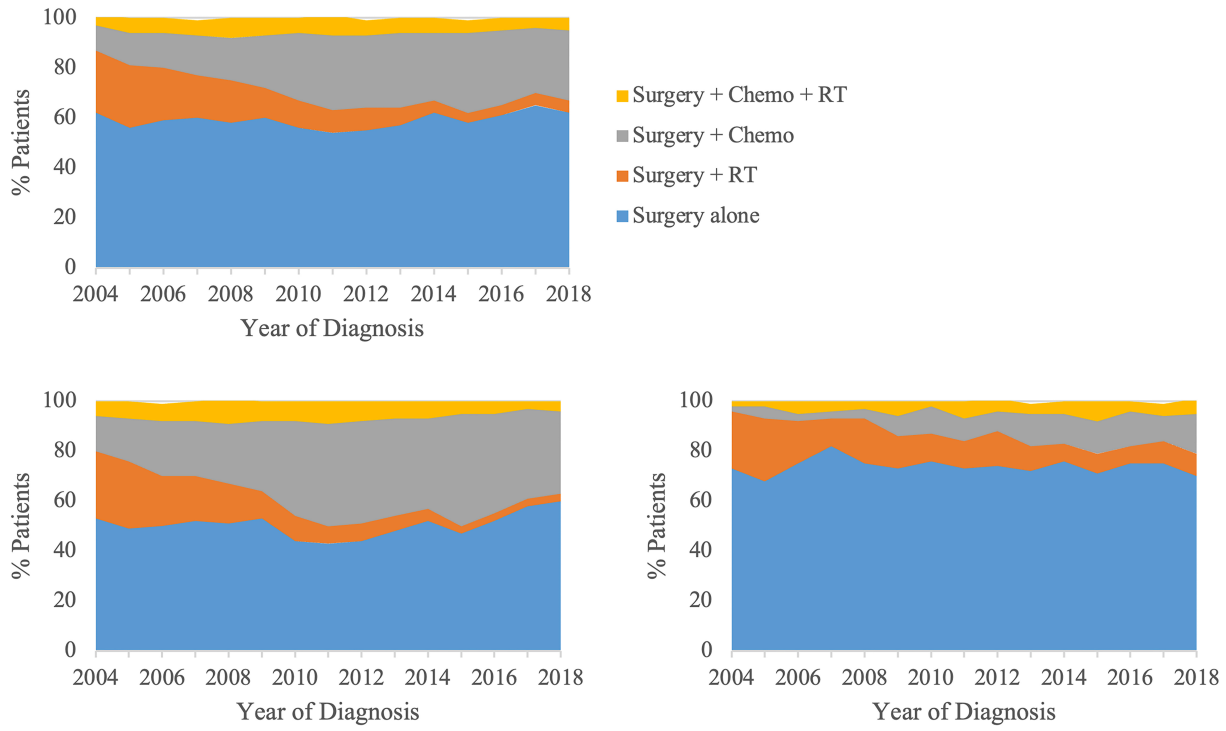

FIGURE 2. Area plot of trends in treatment of uterine sarcomas over time. Top, all histology groups. Bottom left, LMS. Bottom right, AS. RT: radiation therapy.

TABLE 3. Multivariable logistic regression for treatment with radiation therapy.

	Leiomyosarcoma		ESS		Adenosarcoma		Mixed	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age at Diagnosis	1.00	(0.982, 1.017)	1.01	(0.973, 1.041)	1.02	(0.997, 1.041)	0.99	(0.951, 1.020)
Year of Diagnosis	0.86	(0.798, 0.924)***	0.79	(0.675, 0.924)**	0.95	(0.858, 1.047)	0.97	(0.827, 1.142)
Race/Ethnicity								
Non-Hispanic White	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)
Non-Hispanic Black	1.33	(0.911, 1.946)	1.29	(0.510, 3.239)	0.90	(0.500, 1.621)	0.64	(0.228, 1.792)
Hispanic	2.20	(1.317, 3.662)**	1.93	(0.699, 5.302)	1.27	(0.563, 2.854)	2.33	(0.749, 7.219)
Other	2.03	(1.097, 3.739)*	0.54	(0.108, 2.702)	0.53	(0.150, 1.887)	0.53	(0.097, 2.854)
Unknown	0.69	(0.087, 5.552)	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)
Tumor Size								
Smaller than 5 cm	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)
Larger than 5 cm	1.12	(0.677, 1.851)	0.59	(0.289, 1.188)	1.07	(0.609, 1.870)	0.81	(0.228, 2.873)
Stage								
I	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)
II	2.84	(1.960, 4.104)***	3.50	(1.339, 9.168)*	4.89	(2.038, 11.740)***	3.67	(1.250, 10.770)*
III	0.86	(0.532, 1.383)	6.51	(2.985, 14.190)***	1.30	(0.574, 2.926)	0.62	(0.234, 1.632)
IV	1.44	(0.689, 3.018)	5.57	(1.376, 22.510)*	1.00	(1, 1)	0.49	(0.089, 2.759)
Grade								
(0) Well-Differentiated	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)
(1) Moderately-Differentiated	1.34	(0.575, 3.116)	1.08	(0.569, 2.051)	1.60	(0.742, 3.461)	7.39	(0.498, 109.600)
(2) Poorly-Differentiated	2.30	(1.100, 4.791)*	2.07	(0.304, 14.100)	4.15	(2.065, 8.325)***	10.04	(1.066, 94.610)*
(3) Undifferentiated	1.43	(0.663, 3.083)			2.82	(1.367, 5.830)**	8.21	(0.909, 74.02)
LN Dissection								
No LN sampled	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)	1.00	(1, 1)
<7 LN	0.95	(0.617, 1.449)	2.36	(0.984, 5.672)	2.16	(1.030, 4.517)*	1.22	(0.352, 4.253)
≥7 LN	1.42	(1.007, 1.990)*	1.25	(0.597, 2.633)	3.10	(1.692, 5.661)***	2.65	(1.134, 6.195)*

*Exponentiated coefficients, 95% confidence intervals in brackets; *p < 0.05, **p < 0.01, ***p < 0.001. LN: lymph node; ESS: endometrial stromal sarcomas; OR: odds ratio; CI: confidence interval.*

NCDB to elucidate treatment patterns of care and evaluate treatment changes over time for uterine sarcomas, excluding carcinosarcomas. For early stage uterine sarcomas, it is standard of care to undergo a TH+BSO. Approximately 10% of patients in our dataset received TH alone. Some studies have shown BSO has no impact on survival and thus should not be removed, however, this is currently not considered standard of care. While TH+BSO is the standard of care for uterine sarcomas, lymph node sampling is not indicated for uterine sarcomas. The risk of lymph node metastasis is as low as 3% and <10% for LMS and ESS respectfully, and many studies have shown lymphadenectomy has no association with survival [11]. However, there is some discrepancy in lymph node dissection for other uterine sarcomas. Some studies recommend lymph node dissection in high grade ESS [12], while others recommend against it [13, 14]. Patients with obvious extrauterine involvement, clinically suspicious enlarged nodes, or advanced sarcomas may be receiving lymph node sampling. Current practice patterns in the NCDB showed 58% of cases receiving no lymph node sampling and 42% of cases receiving some lymph node sampling.

In our study, the addition of adjuvant chemotherapy was used in almost a third of patients, most commonly with multiagent chemotherapy. There have been no randomized trials showing a survival benefit of chemotherapy in uterine sarcomas. The Gynecologic Oncology Group (GOG) 277 trial attempted to assess if adding doublet chemotherapy to resected uterus with confined LMS provided a survival benefit. Unfortunately, the trial was closed early due to poor accrual, with only 36 of the planned 216 patients enrolled in the study [15]. There did not appear to be a benefit with chemotherapy, although the clinical trial was too low powered to make this conclusion. While chemotherapy agents used are not provided in NCDB, the National Comprehensive Cancer Network (NCCN) first line chemotherapy recommendations include doxorubicin or combination gemcitabine and docetaxel. The NCDB data showed multi-agent chemotherapy was used most often across every histology. These chemotherapy recommendations align more closely with sarcomas than endometrial carcinomas. Thus, collaboration with sarcoma specialists in patients with uterine sarcomas could be beneficial.

The addition of adjuvant RT in treating all uterine sarcoma histologies was not common in our study. The minimal use of adjuvant RT for uterine sarcomas in the NCDB is likely the result of controversial and unclear guidelines for RT in the treatment paradigm of uterine sarcomas. National guidelines recommend the use of RT for AS [16]. While only 16.6% of AS received adjuvant RT in the NCDB, its utilization has been consistent over time. For LMS and high-grade ESS, no phase III trial has shown a benefit to adjuvant RT [8] and national guidelines only suggest considering the use of adjuvant RT. There are minimal and often contradictory recommendations regarding which LMS patients may benefit from adjuvant RT given the low rate, only ~14%, of isolated local only failure [8, 17]. There has been a trend in decreasing utilization of RT in LMS patients. This trend corresponds with the publication of the Phase III randomized trial that did not find a survival benefit with the use of RT in LMS [8]. A recent NCDB study found a similar increase in adjuvant chemotherapy and decrease in RT between the years of 2010 and 2016 [18]. This study also found RT was associated with improved overall survival. While database studies cannot show causation, only association, the association of RT and improved survival is thought provoking. Predictors for the utilization of RT included stage II LMS, high grade ESS and AS, poorly differentiated LMS and AS, as well as, lymph node dissection in LMS, high grade ESS and AS. For stage II uterine sarcomas, RT may be used to help with local control.

When adjuvant RT is utilized, the majority of patients are receiving EBRT. Up to a third of patients received brachytherapy, with two thirds of those patients receiving a brachytherapy boost after EBRT. The recommendations for brachytherapy have varied, from reserving it to LMS patients with cervical extension of disease, to using it in combination with EBRT for all uterine sarcoma patients with stage I–III disease [6]. One institution reported prognostic factors of myometrial invasion greater than 50%, invasion of the uterine cervix, or a small surgical cuff at hysterectomy as indications for adding a brachytherapy boost after EBRT [19].

We recognize there are inherent limitations to database studies including selection bias, limited data on chemotherapies (no information on agents or number of cycles), radiation specifics (treatment volume, treatment breaks) and no endpoints for local control, disease free survival, toxicities, and quality of life outcomes. We are also unable to comment on the prognostic impact of treatments. However, for rare tumors such as uterine sarcomas, database studies provide a large diverse population that is helpful in illustrating treatment patterns amongst these tumors. This study illustrates practice patterns in the treatment of uterine sarcomas and the trends in adjuvant treatment from 2004–2018.

5. Conclusions

This study demonstrates the patterns of care for uterine sarcomas and the trends in treatment management over time. Surgery alone, usually TH+BSO without a lymph node dissection, was the most common treatment modality with no adjuvant treatment. Adjuvant radiation therapy has not commonly been used and has been decreasing over time, especially for LMS.

AVAILABILITY OF DATA AND MATERIALS

Datasets analyzed for this study are through the National Cancer Database, which can found at https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/.

AUTHOR CONTRIBUTIONS

LMB—Conceptualization, Project administration; JK, RH, LMB—Data curation, Formal Analysis; RH and LMB—Methodology; JK—Writing—original draft; JK, RH, KK, KH, DKG, CD, GS and LMB—Writing—review and editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study does not require ethical approval because the data used are properly anonymized and de-identified.

ACKNOWLEDGMENT

The authors would like to thank Kiramey Gilleese for her assistance in editing and formatting for submission.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1647846471991476224/attachment/Supplementary%20material.docx.

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How to cite this article: Jessica Kunzman, Ryan Hutten, Kristen Kelley, Kate Harris, David K. Gaffney, Cristina DeCesaris, *et al*. Treatment patterns for leiomyosarcomas, endometrial stromal sarcomas and adenosarcomas: a national cancer database study. European Journal of Gynaecological Oncology. 2023; 44(2): 25-31. doi: 10.22514/ejgo.2023.019.