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Research Report

Clinicopathologic characteristics and oncologic outcomes in adenosarcoma of gynecologic sites

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ABSTRACT

Objective: To examine clinicopathologic characteristics and oncologic outcomes of patients diagnosed with Mullerian adenosarcoma and to evaluate ovarian preservation as a practical management option in early-stage disease.

Methods: A retrospective review was performed of 31 patients treated for uterine, ovarian, or cervical adenosarcoma at our institution between 1/2000–3/2020. Recurrence-free survival (RFS) and overall survival (OS) were analyzed with Kaplan-Meier estimates, the log-rank test, and Cox proportional hazards regression.

Results: Median age was 51 years (IQR: 41–68). Primary sites included uterine corpus (n = 23, 74.2%), uterine cervix (n = 7, 22.6%), and ovary (n = 1, 3.2%). Surgical management primarily consisted of total hysterectomy +/- bilateral adnexectomy +/- lymph node dissection. Fifteen (48.1%) patients underwent lymph node dissection; no patients had positive nodes. Ovaries were preserved in 6 (19.4%). Twenty-two (71.0%) patients received no adjuvant therapy, 4 (12.9%) received chemotherapy, 1 (3.2%) received chemoradiation, and 3 (9.7%) received hormonal therapy. Sarcomatous overgrowth ($p = 0.04$), high grade histology ($p = 0.002$), and greater depth of myometrial invasion ($p = 0.001$) were associated with decreased RFS. None of the 6 patients with ovarian preservation had recurrences. At last follow up, 21 patients (67.7%) had no evidence of disease, 7 (22.6%) were deceased due to disease, and 3 (9.7%) were deceased due to non-cancerous reasons.

Conclusions: Uterine adenosarcoma appears to have a relatively good prognosis, especially in the absence of risk factors, such as sarcomatous overgrowth, high grade histology, and deep myometrial invasion. Ovarian preservation may be a feasible management option with non-inferior outcomes for premenopausal women with early-stage disease. Future studies including larger patient cohorts are needed for this rare disease.

1. Introduction

Adenosarcoma is a rare gynecologic malignancy representing approximately 1% of female genital tract malignancies and 8% of uterine sarcomas (Nathenson et al., 2016; Bernard et al., 2013). This rare malignancy was first described in the literature by Clement and Scully in 1974 (Clement and Scully, 1974) and are defined as biphasic tumors consisting of benign glandular epithelium and a malignant mesenchymal component, which differentiates these tumors from carcinosarcomas, which have a malignant epithelial component (Nathenson et al., 2016). The epithelial portion typically consists of endometrium-like cells, while the mesenchymal part most commonly consists of low-grade, homologous sarcoma, though may also contain high grade or heterologous mesenchymal elements (Ulrich and Denschlag, 2018). Though these tumors typically arise within the uterine corpus, they can also less commonly originate from the uterine cervix or

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ovary. Adenosarcomas typically have a relatively good prognosis, with recurrences occurring in 26–46% of cases (Bernard et al., 2013; Yuan et al., 2019; Yuan, 2019; Carroll et al., 2014; Tanner et al., 2013). Certain prognostic factors are associated with poorer outcomes. For example, sarcomatous overgrowth, defined as the sarcomatous component occupying more than 25% of the tumor volume, is associated with increased risk of recurrence to as high as 45–70%. Other high-risk features include deep myometrial invasion, heterologous elements and lympho-vascular invasion (LVSI) (Ulrich and Denschlag, 2018; Tanner et al., 2013).

The rarity of the disease is a significant obstacle to obtaining reliable data regarding optimal surgical and medical management, and therefore, treatment recommendations are primarily extrapolated from those of more commonly encountered uterine sarcomas (Nathenson et al., 2016; Tanner et al., 2013; Seagle et al., 2016). Surgical management with hysterectomy and adnexectomy is the mainstay for treatment of adenosarcoma, while the role of staging surgery and adjuvant radiation and/or chemotherapy is much less clear (Carroll et al., 2014; Tanner et al., 2013; Seagle et al., 2016). Further, the safety and feasibility of ovarian preservation remains unclear, though there is evidence of low rates of adnexal metastases among these patients (Taylor et al., 2017). Similarly, fertility preservation for this patient population remains uncertain with limited data based on case reports (Yuan et al., 2019). This study aims to provide a single institution's 20-year experience with management of this rare gynecologic malignancy.

2. Materials and methods

A retrospective review was performed of patients treated for adenosarcoma of gynecologic sites at our institution between January 2000 to March 2020, including patients with uterine, cervical, and ovarian adenosarcoma. This study was approved by the Institutional Review Board (IRB). Patient records were reviewed for demographic information, pathological and clinical staging, oncologic treatment, and oncologic outcomes. Menopausal status was determined by patient report.

2.1. Oncologic treatment

Patients were staged according to the 2009 FIGO staging system. Patients diagnosed before 2009 were re-staged. Surgical management generally consisted of total hysterectomy +/- bilateral salpingo-oophorectomy +/- lymph node dissection. Select patients underwent endometrial polypectomy or myomectomy. All pathologic specimens were interpreted by our institution's subspecialty gynecologic pathologists. The diagnosis of adenosarcoma is defined pathologically by polypoid or phyllodiform proliferation of benign glandular component embedded with sarcomatous growth with periglandular condensation. The proliferating sarcoma cells are generally low grade homologous spindle cells but heterologous component (sex-cord differentiation or high grade rhabdomyosarcoma) can be seen. The sarcomatous overgrowth is defined by the outgrowth of generally high grade pure sarcoma component representing at least 25% of the tumor volume.

Adjuvant therapy was administered on an individual basis and included chemotherapy with or without radiation and hormonal therapy. Adjuvant chemotherapy regimens consisted of 1–6 cycles of ifosfamide/cisplatin, docetaxel/gemcitabine, paclitaxel/ifosfamide, or ifosfamide alone. Hormonal therapies included anastrazole or progesterone IUD.

All patients had routine follow-up with a gynecologic oncologist at our institution and were followed with routine oncologic surveillance. Recurrences were diagnosed by imaging or by biopsy and were categorized as local, regional, or distant.

2.2. Statistical methods

Descriptive statistics regarding patient, tumor, and treatment characteristics were performed. Kaplan Meier methods were used to estimate recurrence free survival (RFS), disease-specific survival (DSS), and overall survival (OS). RFS was calculated from the date of surgery until the date of first recurrence or date of last follow-up. Likewise, DSS and OS were calculated from first date of surgery until the date of death or date of last follow-up. The log-rank test was used to compare RFS, DSS, and OS curves. Predictors of RFS and OS were identified with univariate Cox proportional hazards regression.

Statistical analyses were performed using Stata version 16.

3. Results

Thirty-one patients were identified with adenosarcoma of gynecologic sites. Table 1 summarizes the patient and tumor characteristics, and Table 2 details the treatment characteristics of the patient cohort. Median age was 51 (IQR: 41–68). Fourteen (45.2%) were premenopausal at time of diagnosis, while 1 (3.2%) was perimenopausal, and 14 (45.2%) were postmenopausal. In terms of gynecologic sites, 23 patients (74.2%) had uterine corpus adenosarcoma, 7 (22.6%) had uterine cervix adenosarcoma, and 1 (3.2%) had ovarian adenosarcoma.

3.1. Patient and treatment characteristics: Adenosarcoma of the uterine corpus

Among the 23 patients with uterine corpus adenosarcomas, 21 (91.3%) underwent total hysterectomy, of which 20 (87.0%) additionally underwent bilateral salpingectomy +/- oophorectomy. One patient (4.3%) underwent vaginal myomectomy, and 1 (4.3%) underwent D&C/polypectomy. A total of 4 patients had ovaries preserved. Twelve (52.2%) underwent lymph node dissection. Twelve (52.2%) were stage IA, 7 (30.4%) were IB, 2 (8.7%) were IC, 1 (4.4%) was IIIA, and 1 (4.4%) was IVB. With regards to adjuvant therapy, 16 patients (69.6%) received none, 4 (17.4%) received chemotherapy alone, and 3 (13.0%) received hormonal therapy.

On pathology, 18 patients (78.3%) had homologous elements, while 5 (21.7%) had heterologous elements. Six patients (26.1%) had high grade tumors. Six patients (26.1%) had low mitotic index, 7 (30.4%) were found to have high mitotic index, and 10 (43.5%) did not have a reported mitotic index. Necrosis was present in 11 patients (47.8%). Thirteen patients (56.5%) had no myometrial invasion, 5 (21.7%) had <50% invasion, and 4 (17.4%) had greater than 50% invasion. Four patients (17.4%) were found to have LVSI, and sarcomatous overgrowth was found in 8 patients (34.8%).

Median follow-up was 26 months (IQR: 13–84 months). None of the 4 patients with ovarian preservation had recurrences. Five patients (27.2%) had a recurrence, with median time to recurrence ranging from 2 months to 27 months. Of the 5 recurrences, 1 had a local and regional recurrence, 1 had regional only, 2 had distant only, and 1 had distant and regional. All 5 patients with recurrence died from disease.

3.2. Patient and treatment characteristics: Adenosarcoma of the uterine cervix

All 7 patients with cervical adenosarcoma underwent total hysterectomy, of which 1 (14.3%) underwent additional unilateral adnexectomy and 6 (85.8%) underwent bilateral salpingectomy +/- oophorectomy. Two patients (28.6%) had ovaries preserved. Three (42.9%) underwent lymph node dissection. Six (85.7%) were stage IA, and 1 (14.3%) was IB. No patients with cervical adenosarcoma received adjuvant therapy.

On pathology, 5 patients (71.4%) had homologous elements, while 2 (28.6%) had heterologous elements. Six patients (85.7%) had low grade tumors, while grade was not available for 1 patient (14.3%). Six patients (85.7%) had low mitotic index, and 1 (14.3%) was found to have high mitotic index. One patient (14.3%) had superficial stromal invasion, while the other 6 (85.7%) had no stromal invasion. No patients were

Table 1
Patient and tumor characteristics.

Characteristic	Median (IQR)/n (%) All patients (N = 31)	Uterus (N = 23)	Cervix (N = 7)	Ovary (N = 1)
Age	51 (41–68)	53 (41–74)	45 (42–56)	41
BMI	31.1 (24.9–39.6)	31.1 (24.5–39.6)	33.8 (24.9–40.5)	25
Parity	2 (0–3)	2 (0–3)	1 (0–2)	4
Race				
White, Non-Hispanic	19 (61.3%)	17 (73.9%)	2 (28.6%)	0 (0.0%)
Black, Non-Hispanic	8 (25.8%)	6 (26.1%)	1 (14.3%)	1 (100.0%)
Hispanic	3 (9.7%)	0 (0.0%)	3 (42.9%)	0 (0.0%)
Unknown	1 (3.2%)	0 (0.0%)	1 (14.3%)	0 (0.050
Menopausal Status				
Premenopausal	14 (45.2%)	8 (34.8%)	5 (71.4%)	1 (100.0%)
Perimenopausal	1 (3.2%)	1 (4.3%)	0 (0.0%)	0 (0.0%)
Postmenopausal	14 (45.2%)	12 (52.2%)	2 (28.6%)	0 (0.0%)
Unknown	2 (6.5%)	2 (8.7%)	0 (0.0%)	0 (0.0%)
Stage				
IA	18 (58.1%)	12 (52.2%)	6 (85.7%)	0 (0.0%)
IB	8 (25.8%)	7 (30.4%)	1 (14.3%)	0(0.0%)
IC	2 (6.5%)	2 (8.7%)	0 (0.0%)	0 (0.0%)
IIA	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IIB	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IIIA	1 (3.2%)	1 (4.4%)	0 (0.0%)	0 (0.0%)
IIIB	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IIIC	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
IVA	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IVB	1 (3.2%)	1 (4.4%)	0 (0.0%)	0 (0.0%)
Tumor size (cm)	4.0 (2.7–7.5)	4.5 (3.1–7.5)	2.5 (1.8–3.5)	9.0
Sarcoma type				
Homologous	23 (74.2%)	17 (73.9%)	5 (71.4%)	1 (100.0%)
Heterologous	7 (22.6%)	5 (21.7%)	2 (28.6%)	0 (0.0%)
N/A	1 (3.2%)	1 (4.3%)	0 (0.0%)	0 (0.0%)
Grade				
Low grade	18 (58.1%)	12 (52.2%)	6 (85.7%)	0 (0.0%)
High grade	6 (19.4%)	6 (26.1%)	0 (0.0%)	0 (0.0%)
N/A	7 (22.6%)	5 (21.7%)	1 (14.3%)	1 (100.0%)
Mitotic Index				
Low (<10/10 hpf)	13 (41.9%)	6 (26.1%)	6 (85.7%)	1 (100.0%)
High (10–22/10 hpf)	8 (25.8%)	7 (30.4%)	1 (14.3%)	0 (0.0%)
N/A	10 (32.3%)	10 (43.5%)	0 (0.0%)	0 (0.0%)
Necrosis				
Not present	19 (61.3%)	12 (52.2%)	7 (100.0%)	0 (0.0%)
Present	12 (38.7%)	11 (47.8%)	0 (0.0%)	1 (100.0%)
Myometrial Invasion				
0%	12 (67.7%)	12 (54.6%)	0 (0.0%)	0 (0.0%)
<50%	5 (16.1%)	5 (21.7%)	0 (0.0 %0	0 (0.0%)
=>50%	5 (16.1%)	5 (21.7%)	0 (0.0%)	0 (0.0%)
N/A	9 (29.0%)	1 (4.3%)	7 (100.0%)	1 (100.0%)
Lymphovascular Invasion				
No	12 (38.7%)	11 (61.1%)	1 (14.3%)	0 (0.0%)
Yes	4 (12.9%)	4 (22.2%)	0 (0.0%)	0 (0.0%)
N/A	15 (48.4%)	3 (16.7%)	6 (85.7%)	1 (100.0%)
Sarcomatous Overgrowth				
No	22 (71.0%)	15 (65.2%)	7 (100.0%)	0 (0.0%)
Yes	9 (29.0%)	8 (34.8%)	0 (0.0%)	1 (100.0%)
Hormone Receptor Status				
ER-/PR-	2 (6.5%)	2 (8.7%)	0 (0.0%)	0 (0.0%)
ER+/PR+	9 (29.0%)	7 (30.4%)	2 (28.6%)	0 (0.0%)
Not tested	20 (64.5%)	14 (60.9%)	5 (71.4%)	1 (100.0%)
Surgical Margin				
Negative	28 (90.3%)	20 (87.0%)	7 (100.0%)	1 (100.0%)
Positive	2 (6.5%)	2 (8.7%)	0 (0.0%)	0 (0.0%)
vN/A	1 (3.2%)	1 (4.3%)	0 (0.0%)	0 (0.0%)
Adenomyosis				
Yes	12 (38.7%)	7 (30.4%)	3 (42.9%)	0 (0.0%)
No	19 (61.3%)	16 (69.6%)	4 (57.1%)	1 (100.0%)
Follow up (months)	26 (13–83)	25 (10–104)	33 (20–50)	76

Table 2
Treatment characteristics.

	All patients (N = 31)	Uterus (N = 23)	Cervix (N = 7)	Ovary (N = 1)
Surgery				
Endometrial polypectomy/D&C/ myomectomy	2 (6.5%)	2 (8.7%)	0 (0.0%)	0 (0.0%)
Bilateral SO only	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Hysterectomy only	1 (3.2%)	1 (4.3%)	0 (0.0%)	0 (0.0%)
Hysterectomy + unilateral SO	1 (3.2%)	0 (0.0%)	1 (14.3%)	0 (0.0%)
Hysterectomy + bilateral salpingectomy +/- oophorectomy	11 (35.5%)	8 (34.8%)	3 (42.9%)	0 (0.0%)
Hysterectomy + bilateral salpingectomy +/- oophorectomy + LND	15 (48.4%)	12 (52.2%)	3 (42.9%)	0 (0.0%)
Ovarian Preservation				
No	25 (80.6%)	19 (82.6%)	5 (71.4%)	1 (100.0%)
Yes	6 (19.4%)	4 (17.4%)	2 (28.6%)	0 (0.0%)
Adjuvant Therapy				
None	23 (74.2%)	16 (69.6%)	7 (100.0%)	0 (0.0%)
Chemotherapy	4 (12.9%)	4 (17.4%)	0 (0.0%)	0 (0.0%)
Chemoradiation	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Hormone therapy	3 (9.7%)	3 (13.0%)	0 (0.0%)	0 (0.0%)

found to have necrosis. No patients had sarcomatous overgrowth.

Median follow-up was 33 months (IQR: 20–50). Only one patient (14.3%) had a recurrence after 35 months of follow-up. She had a recurrence in the right psoas and eventually died from disease.

3.3. Patient and treatment characteristics: Adenosarcoma of the ovary

One patient had ovarian adenosarcoma. She underwent bilateral adnexectomy and tumor debulking. She was found to be stage IIIC. She had a homologous tumor, low mitotic index, necrosis, and sarcomatous overgrowth. As adjuvant therapy for her extensive pelvic disease, she received chemotherapy (6 cycles of ifosfamide and paclitaxel) and interstitial brachytherapy with markers placed in the cervix. She was followed for 29 months in total and experienced a recurrence at 27 months in the lung. She proceeded with palliative care and died from disease.

3.4. Oncologic outcomes

Median follow-up for the entire cohort was 26 months (IQR 13–83). Two-year RFS and DSS for the cohort was 86% and 88%, respectively. At last follow up, 21 patients (67.7%) had no evidence of disease, 7 (22.6%) were deceased due to disease, and 3 (9.7%) were deceased due to non-cancerous reasons.

Table 3 summarizes the unadjusted hazard ratios for RFS and OS. On univariate analysis, greater tumor size (HR 1.23, 95% CI 1.04–1.44, p = 0.013), higher grade (HR 10.59, 95% CI 1.07–104.78, p = 0.044, the presence of necrosis (HR 12.91, 95% CI 1.53–108.57, p = 0.019), greater depth of myometrial invasion (HR 1.04, 95% CI 1.01–1.07, p = 0.003), and sarcomatous overgrowth (HR 6.84, 95% CI 1.32–35.31, p = 0.022) predicted for poorer RFS. OS was predicted on univariate analysis by tumor size (HR 1.20, 95% CI 1.05–1.37, p = 0.009), higher grade (HR 11.51, 95% CI 1.90–69.86, p = 0.008), the presence of necrosis (HR 18.10, 95% CI 2.27–144.13, p = 0.006), greater depth of myometrial invasion (HR 1.05, 95% CI 1.02–1.07, p < 0.001), and sarcomatous overgrowth (HR 4.37, 95% CI 1.22–15.59, p = 0.023).

3.5. Treatment of recurrence

Table 4 details the management and disease course for patients who had a recurrence. Of the 7 patients with recurrence, 4 patients underwent surgery, of which 2 received additional chemotherapy and 1 received additional chemoradiation. Two patients received chemotherapy alone, and one patient was treated with palliative care only. Median survival after recurrence was 7 months (IQR: 4–14).

4. Discussion

In this study, we examined the clinicopathologic characteristics, treatment patterns, and oncologic outcomes of patients with uterine, cervical, and ovarian adenosarcoma treated at our institution over 20 years. Further, we aimed to evaluate the safety and feasibility of ovarian preservation in presumed uterine-confined disease for premenopausal patients.

Table 3
Univariate analysis of recurrence-free survival (RFS) and overall survival (OS).

Characteristic	RFS HR (95 CI)	P	OS HR (95 CI)	P
Age	0.98 (0.94–1.03)	0.428	0.996 (0.96–1.03)	0.834
BMI	1.00 (0.92–1.09)	0.945	0.99 (0.91–1.07)	0.749
Tumor location				
Uterus	Reference		Reference	
Cervix	0.62 (0.07–5.37)	0.664	0.41 (0.05–3.34)	0.403
Ovary	2.64 (0.30–23.05)	0.379	1.80 (0.22–14.76)	0.585
Stage				
IA	Reference		Reference	
IB/IC	6.15 (0.63–59.42)	0.117	5.74 (1.09–30.38)	**0.040**
III/IV	27.90 (2.87–271.48)	**0.004**	16.83 (2.60–108.78(	**0.003**
Tumor size	1.23 (1.04–1.44)	**0.013**	1.20 (1.05–1.37)	**0.009**
High grade	10.59 (1.07–104.78)	**0.044**	11.51 (1.90–69.86)	**0.008**
Heterologous vs. homologous type	2.46 (0.548–11.05)	0.240	1.55 (0.38–6.23)	0.537
High vs. low mitotic index	2.22 (0.44–11.18)	0.333	3.01 (0.65–13.81)	0.157
Necrosis	12.91 (1.53–108.57)	**0.019**	18.10 (2.27–144.13)	**0.006**
Myometrial invasion greater than 50%	26.03 (2.53–267.64)	**0.006**	19.26 (3.39–109.76)	**0.001**
Lymphovascular invasion	0.62 (0.18–2.18)	0.460	0.82 (0.28–2.42)	0.716
Sarcomatous overgrowth	6.84 (1.32–35.31)	**0.022**	4.37 (1.22–15.59)	**0.023**
Adjuvant therapy	2.62 (0.58–11.88)	0.209	4.25 (1.21–14.88)	**0.024**

Our findings regarding prognostic factors are generally in agreement with previous studies (Krivak et al., 2001; Kaku et al., 1992; Clement and Scully, 1990). Sarcomatous overgrowth (SO) was significantly associated with decreased RFS and DSS. Compared to a 3-year RFS and DFS of 81% and 90% in patients with no SO, the 3-year RFS and DFS in patients with SO were both 32%. In addition, on univariate analysis, high grade sarcomatous histology, greater depth of myometrial invasion, larger tumor size, and presence of necrosis were significantly associated with decreased RFS and DSS.

The uterine corpus is the most common site of Mullerian adenosarcoma, followed by the uterine cervix. Uterine corpus and cervical adenosarcoma patients are managed similarly, with most authors recommending total hysterectomy with or without adnexectomy. In line with this, 93% of uterine corpus and cervical adenosarcoma patients in our series underwent total hysterectomy. The role of lymphadenectomy for this patient population is not well-defined. Of the 15 patients (12 uterine corpus and 3 cervical) in our series who underwent lymphadenectomy, none were found to have positive nodes. In agreement, the literature demonstrates a low rate of lymph node metastasis, ranging from 0 to 6% (Carroll et al., 2014; Tanner et al., 2013; Seagle et al., 2016; Kaku et al., 1992) and predominantly occurring in those with SO. Furthermore, no overall survival benefit has been demonstrated in uterine adenosarcoma patients following lymphadenectomy (Carroll et al., 2014). As a result, lymphadenectomy is not routinely recommended in this population.

The safety of ovarian preservation for uterine adenosarcoma patients is unclear, with literature primarily confined to case reports (Ozmen, 2007; Michener and Simon, 2001). A SEER study of 968 patients with uterine adenosarcoma reported earlier age of diagnosis in this patient population over the study period, demonstrating the increasing relevance of ovarian and fertility preservation, when and if appropriate (Taylor et al., 2017). Further, previous studies have demonstrated low rates of ovarian metastases in women who have undergone adnexectomy for presumed uterine-confined disease (Carroll et al., 2014; Tanner et al., 2013; Clement and Scully, 1990). In our study, none of the 6 women who were treated with ovary-preserving surgeries had recurrences. Further, of the 24 patients with uterine corpus and cervical adenosarcoma who underwent adnexectomy, none had ovarian metastases. Although we acknowledge this is a small population studied, we believe that ovarian preservation can be considered for premenopausal patients with presumed uterine-confined disease. In further support of this, a National Cancer Database (NCDB) sub-analysis of uterine adenosarcoma patients found no difference in survival between patients who underwent bilateral salpingo-oophorectomy and those who did not (Seagle et al., 2016). The option of ovarian preservation should be mutually decided upon between the patient and the provider after discussion of risks and benefits. A two-phase surgery can also be considered in premenopausal patients, where patients with ER/PR+ tumors undergo a second laparoscopic surgery to remove the ovaries, based on detailed final pathologic examination of the initial specimen.

Fertility preservation is also of concern in this population, as patients can present as young as 13 years (Yuan et al., 2019; Jones and Lefkowitz, 1995). In our cohort, only 2 uterine adenosarcoma patients underwent fertility-sparing surgery (FSS), neither of whom experienced recurrence. Both were good candidates as early stage patients with no SO or myometrial invasion. Case reports have reported successful FSS in early-stage patients with minimal pathologic risk factors such as SO and/or deep myometrial/stromal invasion (L'Heveder, 2019; Togami et al., 2018). A literature review of Mullerian adenosarcoma patients who underwent FSS (16 cervical and 13 uterine) revealed that 6.7% of the cervical and 46.2% of the uterine corpus patients had recurrences (Yuan

Table 4
Characteristics and disease course of patients with recurrence.

Age	FIGO Stage	Tumor location	Surgical treatment	Grade	Sarcoma type	Size (cm)	LVI	MMI (%)	SO	Necrosis	Margins	LN involvement	Adjuvant therapy	RFS (months)	Location of first recurrence	Treatment for first recurrence	Disease course	Status	OS (months)
UTERUS																			
44	IB	Uterus	Total hysterectomy + BSO + LND	Low grade	Homologous	8.5	No	0	No	Present	Negative	None	None	4	Vaginal cuff, pelvis	Tumor debulking, cisplatin/ifosfamide × 6 cycles	Pelvic recurrence -> pelvic exenteration-> deceased from medical complications	Deceased from disease	25
58	IIIA	Uterus	Total hysterectomy + BSO	High grade	Homologous	21	Yes	100	Yes	Present	Positive	N/A	Docetaxel/ gemcitabine × 3 cycles	3	R pelvic sidewall	Tumor debulking, Adriamycin/ ifosfamide × 6 cycles	Progression of peritoneal carcinomatosis -> deceased	Deceased from disease	10
83	IB	Uterus	Total hysterectomy + BSO + LND	N/A	Homologous	1.5	No	45	Yes	Present	Negative	None	None	27	Lung	Palliative care		Deceased from disease	29
38	IVB	Uterus	Total hysterectomy + BSO	High grade	Heterologous (cartilage)	4.5	Yes	100	Yes	Present	Positive	N/A	Ifosfamide × 1 cycle (progressed)	2	Pelvis, peritoneal carcinomatosis	Cisplatin/Adriamycin × 5 cycles	Progression -> gemcitabine/docetaxel	Deceased from disease	6
34	IB	Uterus	Total hysterectomy + BSO + LND	High grade	Heterologous (embryonal rhabdomyosarcoma)	8.3	No	10	Yes	Present	Negative	None	None	14	Lung	Wedge resection of lung	Diffuse metastatic disease -> palliative radiation to spine + chemotherapy -> hospice	Deceased from disease	19
CERVIX																			
45	IA	Cervix	Total hysterectomy + BSO	Low grade	Heterologous (immature cartilage)	2.5	No	N/A	No	N/A	Negative	N/A	None	35	Right psoas	Exploratory laparotomy + tumor debulking, radiotherapy, Adriamycin/ ifosfamide × 6 cycles	Widely metastatic disease -> hospice	Deceased from disease	48
OVARY																			
41	IIIC	Ovary	BSO + transverse loop ostomy	N/A	Homologous	9	N/A	N/A	Yes	Present	Negative	N/A	Interstitial brachytherapy, taxol/ifosfamide × 6 cycles	67	Rectosigmoidpretracheal, axillary, inguinal nodes	Taxol/ifosfamide	Diffuse disease in pelvis -> carboplatin/ doxorubicin -> deceased	Deceased from disease	81

LVI—lymphovascular invasion; MMI—myometrial invasion; SO—sarcomatous overgrowth; LN—lymph node; RFS—recurrence-free survival; OS—overall survival.

et al., 2019), suggesting that FSS may be most feasible among cervical patients. As with ovarian preservation, FSS should be discussed carefully with patients who are deemed appropriate candidates.

There remains no firm consensus on the role of adjuvant chemotherapy and radiation for Mullerian adenosarcoma, though it has been suggested that high-risk patients with SO or deep myometrial invasion should be considered for adjuvant therapy (Nathenson et al., 2016; Arend et al., 2010). A NCDB survival analysis of 2205 patients with uterine, cervical, and ovarian adenosarcoma, of which 100 received adjuvant chemotherapy and 248 received adjuvant radiotherapy, did not find any evidence of a survival benefit associated with adjuvant therapy (Seagle et al., 2016), though there was an acknowledgement that there may have been a bias for women with more invasive disease to receive adjuvant therapy. In our study, 4 uterine corpus patients were treated with adjuvant chemotherapy. Of note, all 4 of these patients had SO, and 2 of the 4 had recurrences. Our results did not appear to provide a clear benefit of adjuvant therapy in preventing recurrent disease. However, it is important to note that it is difficult to draw definitive conclusions from our cohort, given the small cohort, heterogenous and non-standardized treatment regimens that may have been influenced by treatment bias and provider preference.

Hormonal therapies have been considered in management of Mullerian adenosarcomas, given the high frequency of ER and PR receptor expression. ER and PR positivity has been reported in approximately 50–80% of adenosarcomas (Amant et al., 2004; Soslow et al., 2008). There are limited data on use of hormonal therapy for adenosarcoma, though there have been several case reports and series indicating favorable outcomes in patients treated with hormonal therapy (Carroll et al., 2014; Tanner et al., 2013; Hines, 2002; Verschraegen et al., 1998). Within our patient cohort, 81% of patients tested for ER/PR receptor were positive for both receptors. Three patients were treated with hormonal therapy: two with anastrozole and one with the

Mirena IUD. None of the three had any evidence of recurrence. While the data certainly remains limited, hormonal treatments may be considered individually as adjuvant therapy for patients with ER or PR receptor positive adenosarcoma.

The ovary is the most rare tumor site for Mullerian adenosarcoma, and literature on ovarian adenosarcoma is largely limited to case reports (Fukunaga, 1997; Mikami et al., 2004; Shakuntala, 2012; Litta, 2004; Recinos-Money, 2008; Valdez et al., 1979; Sykiotis et al., 2004; Shintaku and Mise, 2012). A case series of 32 ovarian adenosarcoma patients with adequate follow-up demonstrated persistent or recurrent disease in 62.5% (Eichhorn, 2002). Treatment varies widely across cases, though often consists of debulking surgery with varying regimens of adjuvant chemotherapy, radiation, and/or hormonal therapies. An NCDB analysis of 54 ovarian adenosarcoma patients, 44% of whom received adjuvant chemotherapy, did not demonstrate evidence for a survival benefit of chemotherapy (Seagle et al., 2016). The ovarian adenosarcoma patient included in our series presented with advanced disease that was adherent to multiple pelvic structures. She was managed with bilateral adnexectomy with transverse loop ostomy with adjuvant chemotherapy and interstitial brachytherapy. She unfortunately recurred after 27 months of follow-up and eventually died from disease. Small numbers in the literature preclude the ability to offer definitive conclusions about optimal treatment for this more aggressive subtype of Mullerian adenosarcoma.

Optimal treatment for recurrent disease is unclear. Tanner *et al.* and Carroll *et al.* both reported that secondary cytoreduction resulted in improved oncologic outcomes (Carroll et al., 2014; Tanner et al., 2013). In terms of chemotherapy, there have been reported responses to doxorubicin with or without ifosfamide as well as gemcitabine/docetaxel (Bernard et al., 2013; Carroll et al., 2014; Tanner et al., 2013; Verschraegen et al., 1998; Huang et al., 2009; Maeda, 2011), though there is no prospective data. A total of 7 patients (23%) in our cohort had evidence of recurrence. Those with local or regional recurrence (n = 3) were treated with chemotherapy with or without surgery, while distant recurrence (n = 4) was treated with chemotherapy alone or palliation. Unfortunately, all 7 patients with recurrence died from disease. Of note, 5 of the 7 patients had SO and thus the majority had more aggressive disease at the baseline. The small numbers and varied treatment regimens make any conclusions elusive in this area. Based on previous case series, surgery and chemotherapy, particularly doxorubicin-containing regimens, and gemcitabine/docetaxel should certainly be considered in treatment of recurrence.

This study documents our experience in treating an exceedingly rare disease. A strength is that all pathology slides were interpreted by subspecialty gynecologic pathologists. Although the small number of patients vastly limits the power of this study and the ability to draw definitive conclusions, especially with regards to cervical and ovarian adenosarcoma, we believe that this series adds to a limited body of data providing clinical guidance for this rare disease. In summary, standard treatment for uterine and cervical adenosarcoma patients is hysterectomy without lymphadenectomy with consideration of hormone therapy if ER/PR-positive. Ovarian preservation should be considered after extensive counseling in premenopausal patients with presumed uterine-confined disease with an option to remove ovaries after examination of the initial pathological specimen. Because management of adenosarcoma continues to be varied and individualized, reliance on existing clinical experience with consideration of patient preference is crucial. Future studies will continue to contribute our collective knowledge to continue to improve outcomes for patients with Mullerian adenosarcoma.

CRediT authorship contribution statement

Jessie Y. Li: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Levent Mutlu:** Conceptualization, Data curation, Writing – original draft. **Joan Tymon-Rosario:** Conceptualization, Writing – review & editing. **Wafa Khadraoui:** Conceptualization, Writing – review & editing. **Nupur Nagarkatti:** Conceptualization, Writing – review & editing. **Pei Hui:** Conceptualization, Writing – review & editing. **Natalia Buza:** Conceptualization, Writing – review & editing. **Lingeng Lu:** Conceptualization, Writing – review & editing. **Peter Schwartz:** Conceptualization, Methodology, Writing – review & editing. **Gulden Menderes:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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