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Uterine adenosarcoma: an analysis on management, outcomes, and risk factors for recurrence

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Abstract

Objectives—Uterine adenosarcoma is a rare malignancy with little data on optimal management. We aimed to clarify the impact of adjuvant therapy in patients with uterine adenosarcoma and identify risk factors for recurrence and death.

Methods—We performed a retrospective review of patients undergoing primary evaluation and treatment for uterine adenosarcoma at a single institution from July 1982 through December 2011. Univariate and multivariate analyses were used to identify prognostic factors for progression-free (PFS) and overall survival (OS).

Results—We identified 100 patients with uterine adenosarcoma, and 74 patients met the inclusion criteria. On multivariate analysis, sarcomatous overgrowth (SO) and lymphovascular space invasion (LVSI) were predictors of worse PFS and OS. Median PFS and OS were 29.4 and 55.4 months for patients with SO, compared to 105.9 and 112.4 months for patients without SO (PFS HR 2.58, 95% CI 1.37–4.84, $p=0.003$; OS HR 2.45, 95% CI 1.26–4.76, $p=0.008$). Among patients with stage I disease, 17 of 22 patients (77%) with SO and 8 of 37 patients (22%) without SO had recurred ($p<0.001$). Among patients with stage I disease with SO, adjuvant therapy appeared to be associated with longer PFS and OS, but these differences were not statistically significant (PFS, 46.7 vs 29.4 months, $p=0.28$; OS, 97.3 vs 55.4 months, $p=0.18$).

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Conflict of interest

The authors have no conflicts of interest to disclose.

Conclusion—In patients with uterine adenosarcoma, the presence of SO or LVSI confers a higher risk of recurrence. We did not identify an optimal treatment strategy for patients with SO, but adjuvant therapy may be associated with prolonged PFS.

Introduction

Uterine adenosarcoma comprises a group of mixed mesenchymal tumors most commonly arising from the endometrium. These tumors are composed of a benign glandular component intimately associated with a sarcomatous stroma [1]. The sarcomatous component is typically homologous and low grade. Thus, uterine adenosarcoma is considered less aggressive than its high-grade counterpart, carcinosarcoma, and hysterectomy alone is often curative. Uterine adenosarcoma with sarcomatous overgrowth, however, has a malignant potential more akin to that of high-grade sarcoma [2, 3]. Sarcomatous overgrowth is defined as the presence of pure sarcoma occupying at least 25% of the tumor, usually high grade in nature and without a benign glandular component [4]. The reported prevalence of sarcomatous overgrowth in patients with uterine adenosarcoma varies greatly, from 8% to 65% [1–3, 5].

Because of the rarity of uterine adenosarcoma, limited data are available to help guide therapy, and the data that do exist were derived mostly from small retrospective case series and population-based analyses [6, 7]. Hysterectomy is recommended, but the role of staging with lymphadenectomy and/or oophorectomy is uncertain. Recurrent disease has been reported to occur in 26 to 40% of all patients with uterine adenosarcoma after primary therapy [5, 6, 8, 9]; however, patients with sarcomatous overgrowth have a much higher reported rate of recurrence (70%–82%) [2, 3, 5]. To date, it remains unclear what adjuvant treatment should be given to improve outcomes in this population. Additional data are needed to identify risk factors for recurrence and to help determine the best adjuvant treatment strategies for patients with high risk of recurrence from uterine adenosarcoma.

The purpose of this study was to identify risk factors for recurrence and death in patients with uterine adenosarcoma. In addition, we sought to clarify the impact of adjuvant therapy and the roles of oophorectomy and lymphadenectomy in patients with this disease.

Methods

Following approval by the Institutional Review Board of The University of Texas MD Anderson Cancer Center, women who underwent primary evaluation and treatment of uterine AS from July 1982 through December 2011 were identified from our institutional tumor registry. Patients were included if they had a pathologic diagnosis of primary uterine adenosarcoma confirmed by a gynecologic pathologist at MD Anderson and had at least 6 months of follow-up data available. Demographic, clinicopathologic, and treatment data were abstracted from the patient medical records. Stage was assigned on the basis of the International Federation of Gynecology and Obstetrics 2009 criteria [10]. Patients who did not undergo routine lymphadenectomy were assigned a clinical stage on the basis of their available pathology and imaging reports.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. The product-limit method of Kaplan and Meier was used to estimate progression-free survival (PFS) and overall survival (OS) [11]. Survival was determined from the date of surgery for the initially diagnosed uterine adenosarcoma. One patient did not undergo hysterectomy, and OS and PFS were calculated from date of initial biopsy. For PFS, an event was defined as disease progression, recurrence, or death. Cox proportional hazards regression was used to model PFS and OS as functions of potential prognostic factors, including age, cardiovascular disease, prior estrogen or tamoxifen use, history of cancer or previous radiation, stage of disease, lymphovascular space invasion (LVSI), sarcomatous overgrowth or heterologous elements, lymph node assessment, and adjuvant therapy [12]. Patients who had any pelvic or para-aortic lymph nodes removed at the time of surgery were classified as having a lymph node assessment. Patients were considered to have received adjuvant therapy if they were treated with any radiation and/or chemotherapy. Because of the limited number of patients who received hormonal therapy, hormonal therapy was not considered adjuvant therapy and was discussed separately. We also estimated the cumulative incidence of disease-specific survival (DSS) with death from other causes considered a competing event using the methods of Gooley et al [13], and we used the methods of Fine and Gray to estimate the risk of death from disease [14]. A p-value <0.05 was considered statistically significant. All analyses were performed with SAS 9.1 for Windows (SAS Institute Inc., Cary, NC) and STATA 11.0 for Windows (StataCorp LP, College Station, Texas).

Results

We identified 100 patients who had primary evaluation and treatment of uterine adenosarcoma at our institution during the study period. Twenty-six of these patients were excluded because of incomplete follow-up or clinicopathologic information, leaving 74 patients for analysis. The median follow-up time for these 74 patients was 56.5 months (range, 3.3–241.1 months). One patient without 6 months of follow-up who died of disease progression 3.3 months after initial treatment was included in the study.

The patients' demographic and clinical features are summarized in Table 1. The median age at diagnosis was 54 years (range, 15–84 years). The majority of patients were Caucasian (69%) and presented with abnormal uterine bleeding (65%). On preoperative clinical examination, a polyp prolapsing through the cervix was seen in 27 patients (36%). Fifty-nine patients (80%) had stage I disease, 10 (14%) had stage II disease, 3 (4%) had stage III disease, and 2 (3%) had stage IV disease. Seven patients (9%) had documented LVSI, and 67 had either no LVSI or it was not documented. Thirty-one patients (42%) had sarcomatous overgrowth, and 15 patients (20%) had tumors that contained heterologous elements.

Primary treatment

Seventy-two patients (97%) underwent hysterectomy as part of their treatment for uterine adenosarcoma. Two patients did not undergo hysterectomy. One patient was treated with primary radiation therapy and chemotherapy because of a deep venous thrombosis at the time of diagnosis that limited primary surgery. This patient had sarcomatous overgrowth,

and stage III disease was suspected because of significant retroperitoneal lymphadenopathy on imaging. The patient died 7 months after diagnosis. The second patient was 15 years old and was diagnosed with uterine adenosarcoma without sarcomatous overgrowth at the time of polypectomy. This patient was treated with 9 cycles of vincristine, dactinomycin, and cyclophosphamide, followed by a dilation and curettage that showed no residual disease. This patient was disease free at last follow-up, 11 years after polypectomy.

Oophorectomy and lymphadenectomy

Sixty patients (81%) had a bilateral salpingo-oophorectomy either prior to or at the time of surgery for uterine adenosarcoma. Ten patients (17%) had adnexal involvement on final pathology review. Five (8%) of these patients had ovarian metastases without gross extrauterine disease at the time of surgery.. The operative records showed that only 1 of these 5 patients had gross ovarian involvement. Of the 14 patients who did not undergo bilateral salpingo-oophorectomy, 4 (29%) had recurrence of disease, and none had an isolated ovarian recurrence. We used Cox proportional hazards regression to model PFS as a function of BSO (HR = 1.69, 95% CI 0.76 – 3.78, $p=NS$). There were 14 patients without bilateral salpingo-oophorectomy, and 7 of these patients had a PFS event (median PFS = 74.1 months; 5-year PFS = 64.3%, 95% CI 43.5%-95.0%). There were 60 patients with bilateral salpingo-oophorectomy, and 41 of these patients had a PFS event (median PFS = 51.3 months; 5-year PFS = 46.4%, 95% CI 34.8%–61.7%).

Twenty-two patients (30%) had lymphadenectomy at the time of surgery. Only 1 of these patients (4%) was diagnosed with a lymph node micrometastasis. This patient also had sarcomatous overgrowth and disease spread to the adnexa and cervix. Patients who underwent lymphadenectomy showed no improvement in PFS (HR 0.67, 95% CI, 0.35–1.30, $p=0.24$), DSS (HR 1.82, 95% CI 0.82–4.01, $p=0.14$), or OS (HR 0.83, 95% CI 0.41–1.66, $p=0.59$) compared to those without lymphadenectomy on univariate and multivariate analysis.

Adjuvant therapy

In the entire cohort, 47 patients (64%) were treated with surgery alone, and 1 patient was treated with primary radiation therapy and chemotherapy without surgery. Twenty-two patients (30%) received adjuvant chemotherapy and/or radiation therapy, and 4 patients (5%) were treated with adjuvant hormonal therapy (Table 1).

Of the 18 patients who received any radiation therapy, 2 were given vaginal cuff brachytherapy alone, both of whom had stage I disease. The remaining 16 patients were given pelvic external beam radiation therapy alone ($n=7$) or a combination of pelvic external beam radiation therapy with vaginal cuff brachytherapy ($n=9$).

Among the 8 patients who received adjuvant chemotherapy, the most common regimen used was doxorubicin with ifosfamide ($n=3$). The other regimens used were vincristine, dactinomycin, and cyclophosphamide; gemcitabine with docetaxel; single-agent cisplatin; and single-agent liposomal doxorubicin.

Of the 4 patients who received hormonal therapy, 3 were on hormonal agents because of a history of breast cancer at the time of diagnosis of uterine adenosarcoma and were continued on hormonal therapy after surgery for adenosarcoma. The other patient had stage IV adenosarcoma with sarcomatous overgrowth with diffuse strong staining for estrogen and progesterone receptors and was given leuprolide acetate until 1.5 years after surgery, when she experienced a recurrence of adenosarcoma. The patient was switched to anastrozole and ultimately had a complete response. Seven years after the recurrence, the patient remained free of disease, and anastrozole was discontinued. One year after anastrozole was discontinued, the patient again developed recurrent disease in the pelvis and resumed anastrozole. This patient had stable disease at last follow-up, 12.5 years after the initial diagnosis of uterine adenosarcoma. The recurrent tumor demonstrated diffuse strong staining for estrogen and progesterone receptors. The receptor status of the uterine adenosarcoma tumor was unknown for the other 3 patients treated with hormonal agents.

Risk factors for recurrence and death

Factors associated with worse PFS on multivariate analysis were presence of sarcomatous overgrowth (HR 2.58, 95% CI 1.37–4.84, $p=0.003$), LVSI (HR 3.78, 95% CI 1.45–9.86, $p=0.007$), older age at diagnosis (HR 1.02, 95% CI 1.00–1.04, $p=0.016$), and advanced stage (stage II HR 3.14, 95% CI 1.41–6.98, $p=0.005$; stage III HR 24.70, 95% CI 4.95–123.40, $p<0.001$; stage IV HR 8.30, 95% CI 1.79–38.47, $p=0.007$). Factors associated with worse DSS on multivariate analysis were the presence of sarcomatous overgrowth (HR 6.25, 95% CI 1.99–19.68, $p=0.001$), LVSI (HR 4.75, 95% CI 2.21–10.2, $p<0.001$), and stage III disease (HR 16.97, 95% CI 3.51–82.12, $p<0.001$). Factors associated with worse OS on multivariate analysis included the presence of sarcomatous overgrowth (HR 2.45, 95% CI 1.26–4.76, $p=0.008$), LVSI (HR 3.50, 95% CI 1.42–8.63, $p=0.007$), and cardiovascular disease (HR 3.45, 95% CI 1.25–9.47, $p=0.02$).

Sarcomatous overgrowth

As outlined in the preceding section, sarcomatous overgrowth was associated with worse PFS, DSS, and OS on multivariate analysis. Median PFS and OS times were 29.4 months and 55.4 months for those with sarcomatous overgrowth, compared to 105.9 and 112.4 months for those without sarcomatous overgrowth (Figure 1a and 1b). The frequency of sarcomatous overgrowth increased with increasing stage of disease: sarcomatous overgrowth was present in 37% (22/59) of patients with stage I disease, 50% (5/10) of patients with stage II disease, 100% (3/3) of patients with stage III disease, and 50% (1/2) of patients with stage IV disease.

Among patients with stage I uterine adenosarcoma, 32% (7/22) with sarcomatous overgrowth received chemotherapy and/or radiation therapy, compared to only 19% (7/37) without sarcomatous overgrowth. Among patients with stage I adenosarcoma with sarcomatous overgrowth, receipt of adjuvant therapy appeared to be associated with longer PFS, DSS, and OS; however, these differences were not statistically significant (Table 2).

Recurrent disease

Thirty-four patients (46%) experienced recurrence of disease (Table 3). The median time to first recurrence was 18.3 months (range 1.5–89.2 months). Twenty-five of 59 patients (42%) with stage I disease, 6 of 10 patients (60%) with stage II disease, and 3 of 5 patients (60%) with stage III or IV disease had recurrence. Patients with earlier-stage disease had a longer time to first recurrence (median time, 28.1 months for stage I and 9.9 months for stage II vs. 3.1 months for stage III, $p=0.03$). Of the 34 patients with recurrence, 20 (59%) had recurrence within the pelvis only, 11 (32%) had recurrence within the abdomen, 2 (6%) had distant recurrence, and 1 had an unknown site of recurrence. The most common histology of the recurrent tumor was high-grade or unclassified sarcoma in 76% of cases. Only 2 (6%) patients recurred as adenosarcoma.

Twenty-four of the 34 patients with recurrence (71%) had sarcomatous overgrowth at the time of initial diagnosis. In these 24 patients, the initial disease stage was stage I in 17 patients (71%), stage II in 4 patients (17%), stage III in 2 patients (8%), and stage IV in 1 patient (4%). Of these 24 patients with sarcomatous overgrowth and recurrence, 9 (38%) had received adjuvant therapy at the time of initial diagnosis, and 15 (62%) had been treated with surgery alone.

Among patients with stage I uterine adenosarcoma, 17 of 22 patients (77%) with sarcomatous overgrowth had a recurrence compared to 8 of 37 patients (22%) without sarcomatous overgrowth ($p<0.001$). Every patient with sarcomatous overgrowth and stage II, III, or IV disease had a recurrence. The characteristics and treatment for those 22 patients with stage I adenosarcoma with sarcomatous overgrowth is listed in Table 3. Several patients had a prolonged disease-free interval with adjuvant therapy and/or secondary surgery.

Twenty-one of the 34 patients diagnosed with recurrence (62%) underwent secondary cytoreduction. Median OS (from the date of the initial surgery) for those who underwent secondary cytoreduction was 58.4 months, versus 30.1 months for those who did not (HR 0.68, 95% CI 0.28–1.67, $p=0.4$). In the patients who underwent secondary cytoreduction, median survival time from the date of recurrence was 16.1 months, compared to 8.4 months in patients who did not undergo secondary surgery (HR 0.85, 95% CI 0.35–2.08, $p=0.7$). One patient with recurrent stage IV disease was treated with hormonal therapy alone and was alive with disease at last follow-up, 11 years after recurrence. Three patients with recurrence were alive without disease at the end of this study. Two of these patients received doxorubicin with ifosfamide as part of their treatment for recurrent disease.

Discussion

In this study, we identified the presence of sarcomatous overgrowth and LVSI as poor prognostic factors for patients with uterine adenosarcoma. Patients with sarcomatous overgrowth had significantly shorter PFS, DSS, and OS than patients without sarcomatous overgrowth. Sarcomatous overgrowth occurred more frequently at advanced stages of uterine adenosarcoma. Among patients with stage I uterine adenosarcoma, those with sarcomatous overgrowth were more likely to receive adjuvant therapy than were those

without sarcomatous overgrowth. Among patients with stage I uterine adenocarcinoma with sarcomatous overgrowth, adjuvant therapy appeared to increase the time to recurrence; however, this effect was not statistically significant. Our cohort of patients represents one of the largest single-institution cohorts of patients with uterine adenocarcinoma published to date and has the largest representation of patients with sarcomatous overgrowth [2, 3, 7]. Despite this, the overall low incidence of this disease makes outcomes analyses and those regarding optimal treatment challenging. Additionally, the staging of uterine adenocarcinoma was changed in the 2009 International Federation of Gynecology and Obstetrics staging system, making comparisons to previous studies difficult.

Our findings regarding prognostic factors for recurrence and survival are in agreement with findings from previous studies. The presence of deep myometrial invasion, sarcomatous overgrowth, heterologous elements, LVSI, and advanced stage have all been linked with a worse prognosis [2, 5, 8, 9]. The presence of sarcomatous overgrowth has been shown to be associated with higher rates of recurrence and decreased OS [5]. Similarly, our analysis found that the presence of sarcomatous overgrowth and LVSI were both associated with worse PFS, DSS, and OS on multivariate analysis. Additionally, advanced stage was associated with poor PFS and DSS, but the small number of patients in this cohort limited survival comparisons. Older age at diagnosis was also associated with worse PFS on multivariate analysis. A 2% increase in recurrence risk was found with each year of advancing age. Our analysis did not show worse outcomes in patients with deep myometrial invasion or heterologous elements, but these results are limited because of the small number of patients with these characteristics.

A small percentage of patients with uterine adenocarcinoma will present at a young age, and it is important to address the role of fertility preservation in this disease. Our retrospective study included a 15-year-old patient who had a polypectomy with adjuvant chemotherapy. At last follow-up, this patient had been disease free for nearly 11 years. One of the largest published series of patients with uterine adenocarcinoma, a series of 100 patients reported by Clement and Scully, included 4 patients treated with only a polypectomy and/or dilation and curettage [9]. Two of these 4 patients had recurrence, and both of these patients had the recurrence treated with local resection. One of the patients was lost to follow-up, and the other was without evidence of disease 11.5 years after the treatment for recurrence. Another case series by Zaloudek and Norris, included 2 patients treated with local resection; these patients were without disease 4 and 6 years, respectively, after surgery [8]. While it is difficult to draw conclusions from the limited number of young patients, local resection with or without adjuvant chemotherapy can be considered for young patients who desire future fertility.

The benefit of lymphadenectomy in patients with uterine adenocarcinoma is a subject of debate. In our cohort, of the 24 patients who underwent lymphadenectomy, only 1 (4%) was diagnosed with lymph node metastasis, which was a micrometastasis. This patient had sarcomatous overgrowth and disease spread to the adnexa and cervix. Few reports in the literature have commented on lymph node involvement in uterine adenocarcinoma. In 3 of the largest studies to date, 0 of 11 (0%), 2 of 31 (6%), and 0 of 9 (0%) patients had lymph node metastasis [5, 7, 9]. A study of 11 patients with adenocarcinoma and sarcomatous overgrowth

included 3 patients with positive nodes, 2 of whom had grossly enlarged nodes [3]. All patients with positive nodes in our study and these previous studies were patients with sarcomatous overgrowth. A separate analysis of the Surveillance, Epidemiology, and End Results (SEER) database reported nodal metastases in 3.1% of 262 women who underwent a lymphadenectomy for adenosarcoma, but whether or not women with nodal metastases had sarcomatous overgrowth was not specified [6]. The reported experiences to date indicate that lymphadenectomy may not be necessary for staging all patients with uterine adenosarcoma. Patients with sarcomatous overgrowth are more likely to have nodal metastases, but they are also more likely to have other high-risk features, such as deep myometrial invasion, LVSI, and higher-stage disease [5], that would indicate a worse prognosis and alert clinicians to consider adjuvant therapy regardless of nodal status.

The role of ovarian preservation in patients with uterine adenosarcoma is also unclear. In our cohort, 5 of 60 patients (8%) that underwent bilateral salpingo-oophorectomy had ovarian metastases without any other evidence of extrauterine disease. One patient had grossly abnormal adnexa, 2 patients had normal-appearing ovaries, and in the other 2 cases, the operative note did not specify the appearance of the ovaries. Previous studies have also reported a low risk of ovarian metastases in patients with uterine adenosarcoma. In the largest published study of uterine adenosarcoma, only 2 of 100 patients had adnexal involvement, and both of these had grossly abnormal adnexa [9]. In a recent series reported by Tanner et al, of 19 patients who had their initial surgery at Memorial Sloan-Kettering Cancer Center, none of the patients had ovarian involvement [7]. Given the overall low rates of ovarian metastases reported to date, ovarian preservation in premenopausal women with uterine adenosarcoma appears to be a reasonable option in the absence of gross involvement. However, physicians must fully discuss with patients the risks and benefits of ovarian preservation because the role of estrogen in the progression or recurrence of this disease is uncertain.

Some authors have advocated hormonal therapy for treatment of uterine adenosarcoma. Pathologic analyses of uterine adenosarcoma have identified estrogen receptor positivity in approximately 80% of cases and progesterone receptor positivity in 65% to 80% of cases; however, the incidence of hormone receptor positivity is lower in patients with sarcomatous overgrowth [15, 16]. Reports of successful treatment of uterine adenosarcoma with hormonal therapy are limited [7,17, 18]. In our series, 3 patients with uterine adenosarcoma were coincidentally taking hormonal agents for a previous diagnosis of breast cancer. Two of these patients had no evidence of recurrence on therapy, and the other had prolonged stable disease on therapy. Although data are limited, the reports to date indicate that hormonal agents can be considered for adjuvant therapy on an individualized basis in patients with uterine adenosarcoma.

Surgery is the primary means of treating uterine adenosarcoma; however, there has been no consensus on the use of adjuvant chemotherapy or radiation therapy for this disease. Adjuvant chemotherapy for uterine adenosarcoma has typically included sarcoma-based regimens, use of which has been associated with varying degrees of success [8, 19]. Small series suggest that radiation therapy may be effective in preventing local recurrence of uterine adenosarcoma; however, these data are limited [2, 7, 9, 20]. In the largest published

series of women with uterine adenocarcinoma, based on the SEER database, no survival benefit was seen in 111 of 544 women treated with adjuvant radiation [6]. In our cohort, no specific adjuvant therapy led to a significant improvement in PFS or OS. However, among patients with stage I uterine adenocarcinoma with sarcomatous overgrowth, those who received adjuvant therapy appeared to have longer PFS, DSS, and OS, although these differences were not statistically significant. Several patients with stage I adenocarcinoma with sarcomatous overgrowth who received adjuvant therapy had remote recurrences up to 7 years after their initial diagnosis. Given the high risk of recurrence in patients with sarcomatous overgrowth, adjuvant therapy may be considered for this population.

Optimal treatment for recurrent uterine adenocarcinoma remains uncertain. Tanner et al reported increased time to second recurrence (12.7 vs. 29.7 months) in patients who underwent secondary cytoreduction at the time of first recurrence, but this increase was not statistically significant [7]. In our study, among patients with first recurrence, the median OS for patients who underwent secondary cytoreduction was 58.4 months, versus 30.1 months for patients who did not undergo secondary cytoreduction; however, this difference was not statistically significant. Those patients who underwent a secondary cytoreduction also had a longer time to first recurrence than those patients that did not have surgery after recurrence of disease. There may be a selection bias due to improved tumor biology in those patients with disease amenable to resection after recurrence. Overall, our study had limited power to evaluate the benefit of secondary surgery. In patients with recurrence, doxorubicin with ifosfamide was the only chemotherapy regimen to produce a complete response: 2 patients treated with this regimen were free of disease 1 and 5 years, respectively, after recurrence. Tanner et al reported similar response rates to doxorubicin with ifosfamide after recurrence [7]. Thus, treatment of recurrence with secondary cytoreduction followed by doxorubicin and ifosfamide is reasonable in patients with good performance status and limited disease amenable to surgical resection.

Our study is one of the largest series to report long-term outcomes of patients with uterine adenocarcinoma. Another strength of our study is that all cases of uterine adenocarcinoma were reviewed by a gynecologic pathologist at MD Anderson to confirm the diagnosis. Though our study is limited by its retrospective nature and the inherent biases of retrospective studies, much can be gleaned from our experience with this rare tumor. Most patients with uterine adenocarcinoma are diagnosed at an early stage and have an excellent prognosis with surgery alone, but those with sarcomatous overgrowth and advanced stage are at a much higher risk of recurrence and death. Premenopausal women who prefer ovarian preservation should be counseled about the small risk of residual microscopic disease and the uncertainty of the role of estrogen and progesterone receptors in uterine adenocarcinoma. The overall rate of lymph node metastasis in patients with uterine adenocarcinoma is low, and routine lymphadenectomy may be omitted in initial surgical management. However, grossly enlarged nodes should be removed. Adjuvant therapy with sarcoma-based chemotherapy regimens such as doxorubicin and ifosfamide may be considered in patients at high risk for recurrence or death, such as patients with sarcomatous overgrowth and those with advanced or recurrent disease. Future studies will add to the collective knowledge of uterine adenocarcinoma and assist with management of this rare disease.

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Research highlights

In women with uterine adenosarcoma, sarcomatous overgrowth is associated with worse progression-free, disease-specific, and overall survival.

Surgical management of uterine adenosarcoma does not require routine lymphadenectomy as lymph node metastases are rare.

Uterine adenosarcoma can recur many years after initial diagnosis, and thus prolonged surveillance of patients with this disease is necessary.

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Figure 1.
a. Kaplan-Meier curves for progression-free survival in patients with uterine adenosarcoma with and without sarcomatous overgrowth
Median PFS was 29.4 months for those patients with AS with SO, 105.9 months for those patients with AS without SO (HR 2.58, 95% CI 1.37–4.84, p=0.003)
b. Kaplan-Meier curves for overall survival in patients with uterine adenosarcoma with and without sarcomatous overgrowth

Median OS was 55.4 months for those patients with AS with SO, 112.4 months for those patients with AS without SO (HR 2.45, 95% CI 1.26–4.76, $p=0.008$).

Table 1

Clinical and demographic data for 74 patients with uterine adenosarcoma

Variable	No. of patients (%)
Age, median (range)	54 years (15–84 years)
Weight, median (range)	82 kg (45–168 kg)
Race/ethnicity	
Caucasian	51 (69)
African American	13 (18)
Latina	9 (12)
Other	1 (1)
Presenting symptom	
Abnormal bleeding	48 (65)
Pelvic pain	9 (12)
Other	17 (23)
Examination findings	
Polyp	27 (36)
Pelvic mass	10 (14)
Other	37 (50)
Stage	
I	59 (80)
II	10 (14)
III	3 (4)
IV	2 (3)
Tumor size, median (range)	6.0 cm (0.1–11 cm)
Depth of invasion	
None	19 (26)
50%	24 (32)
>50%	1 (1)
Unknown	30 (41)
Lymphovascular space invasion	
Present	7 (9)
Absent	67 (91)
Sarcomatous overgrowth	
Present	31 (42)
Absent	43 (58)
Heterologous elements	
Present	15 (20)
Absent	59 (80)
Primary treatment	
Chemotherapy + radiation	1 (1)
Surgery alone	47 (64)
Surgery + radiation	14 (19)

Variable	No. of patients (%)
Surgery + chemotherapy	5 (7)
Surgery + chemotherapy + radiation	3 (4)
Surgery + hormones	4 (5)

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Table 2

Progression-free (PFS), disease-specific (DSS), and overall survival (OS) for patients with stage I uterine adenosarcoma stratified by sarcomatous overgrowth (SO) and receipt or nonreceipt of adjuvant therapy

Patient subset	n	Median survival time, mo	p value	Hazard ratio	95% CI
PFS					
Stage I with SO					
Surgery alone	15	29.4	—	Ref	—
Surgery + adjuvant	7	46.7	0.28	0.58	0.22–1.56
All stage I					
Surgery alone	45	67.2	—	Ref	—
Surgery + adjuvant	14	89.2	0.63	0.82	0.37–1.82
DSS					
Stage I with SO					
Surgery alone	15	61.3	—	Ref	—
Surgery + adjuvant	7	97.3	0.46	0.67	0.23–1.96
All stage I					
Surgery alone	45	NR	—	Ref	—
Surgery + adjuvant	14	NR	0.82	1.12	0.42–3.01
OS					
Stage I with SO					
Surgery alone	15	55.4	—	Ref	—
Surgery + adjuvant	7	97.3	0.18	0.45	0.14–1.44
All stage I					
Surgery alone	45	81.6	—	Ref	—
Surgery + adjuvant	14	112.4	0.27	0.61	0.25–1.48

Adjuvant = adjuvant chemotherapy and/or radiation therapy; NR = not reached.

Table 3

Demographic and clinical characteristics, treatment, and outcomes for patients with recurrence of uterine adenocarcinoma (n=34)

Age, yr	Stage	SO	LYSI	Initial adjuvant therapy after hysterectomy	Histology of recurrence	Site of recurrence	Time to 1st recurrence, mo	Treatment of 1st recurrence	Disease response	Survival after 1st recurrence, mo	Status at last follow-up
61	I	Y	N	None	High-grade sarcoma	Pelvis	67.8	EBRT	PD	1.9	DOD
80	I	Y	Y	None	Unclassified sarcoma	Distant	28.1	Surgery + hormones	PD	27.4	DOD
58	I	Y	N	None	High-grade sarcoma	Pelvis	9.0	Surgery + EBRT + brachy	CR	12.3	DOD
51	I	Y	N	EBRT + brachy	High-grade sarcoma	Pelvis	75.5	Doxorubicin + ifosfamide	PR	21.8	DOD
70	I	Y	N	None	Unclassified sarcoma	Pelvis	74.1	Surgery + hormones	PD	7.5	DOD
53	I	Y	N	None	Unclassified sarcoma	Abdomen	29.5	Surgery + doxorubicin + carboplatin	CR	31.9	DOD
60	I	Y	N	None	High-grade sarcoma	Pelvis	25.4	Surgery + doxorubicin + ifosfamide	PD	13.7	DOD
79	I	Y	Y	None	Unclassified sarcoma	Pelvis	4.5	Surgery + hormones	CR	42.0	DOD
59	I	Y	N	None	High-grade sarcoma	Pelvis	62.7	Surgery + hormones	CR	69.1	DOD
61	I	Y	N	Doxorubicin + ifosfamide	Unclassified sarcoma	Pelvis	89.3	Surgery + gemcitabine + docetaxel	PR	5.5	DOD
78	I	Y	N	EBRT + brachy	High-grade sarcoma	Pelvis	41.4	Doxorubicin	PD	6.7	DOD
67	I	Y	Y	None	Unknown	Pelvis	8.8	Doxorubicin + DTIC	PR	10.1	DOD
43	I	Y	N	EBRT	High-grade sarcoma	Abdomen	14.3	Doxorubicin + DTIC	PR	15.8	DOD
62	I	Y	N	Unknown chemo	High-grade sarcoma	Abdomen	46.7	Surgery + carboplatin + paclitaxel	CR	66.6	AWD
55	I	Y	N	Brachy	High-grade sarcoma	Pelvis	30.2	Surgery + EBRT	CR	41.9	DOD
55	I	Y	Y	None	High-grade sarcoma	Pelvis	2.5	Doxorubicin	PD	1.1	DOD
56	I	Y	N	None	High-grade sarcoma	Distant	12.2	Surgery + EBRT + carboplatin + paclitaxel	PD	3.9	AWD
36	II	Y	N	EBRT + brachy	Unknown	Unknown	23.9	Unknown		2.3	DOD
44	II	Y	N	Doxorubicin + ifosfamide	Unclassified sarcoma	Abdomen	17.1	Unknown		38	DOD
40	II	Y	Y	None	Unclassified sarcoma	Abdomen	2.7	None	PD	0.6	DOD
49	II	Y	N	None	Adenosarcoma	Pelvis	51.3	Surgery + EBRT + brachy	CR	54.2	AWD
60	III	Y	Y	None	Unknown	Pelvis	2.5	none	PD	2.9	DOD
36	III	Y	N	EBRT	High-grade sarcoma	Abdomen	3.8	Surgery + liposomal doxorubicin	PD	14.0	DOD

Age, yr	Stage	SO	LYSI	Initial adjuvant therapy after hysterectomy	Histology of recurrence	Site of recurrence	Time to 1st recurrence, mo	Treatment of 1st recurrence	Disease response	Survival after 1st recurrence, mo	Status at last follow-up
47	IV	Y	N	Leuprolide acetate	Unclassified sarcoma	Pelvis	16.8	Hormones	CR	117.0	AWD
68	I	N	N	Brachy	Unclassified sarcoma	Abdomen	44.5	Hormones	PD	3.2	DOD
68	I	N	N	None	High-grade sarcoma	Pelvis	9.9	Surgery + VAC + DTIC	CR	12.8	Died of other cause
73	I	N	N	None	Unknown	Pelvis	11.9	Surgery + interstitial gold seeds	CR	16.1	Died of other cause
44	I	N	N	None	Unclassified sarcoma	Abdomen	76.3	AC + DTIC + surgery	CR	13.2	Died of other cause
47	I	N	N	None	High-grade sarcoma	Pelvis	13.3	Surgery with IORT + EBRT	CR	8.3	DOD
67	I	N	N	None	Heterologous sarcoma	Pelvis	42.4	Surgery + EBRT	CR	13.2	DOD
32	I	N	N	None	Unclassified sarcoma	Abdomen	11.9	Doxorubicin + ifosfamide	PR	20.4	DOD
54	I	N	N	None	High-grade sarcoma	Abdomen	19.5	Unknown		1.0	NED
52	II	N	N	EBRT with cisplatin	Adenosarcoma	Pelvis	2.1	Gemcitabine + docetaxel	CR	62.8	NED
51	II	N	N	None	Unknown	Abdomen	1.5	Vincristine + doxorubicin + ifosfamide	CR	16.5	NED

SO = sarcomatous overgrowth; LYSI = lymphovascular space invasion; Y = yes; N = no; PD = progressive disease; PR = partial response; CR = complete response; DOD = dead of disease; AWD = alive with disease; NED = no evidence of disease; VAC = vincristine, doxorubicin, and cyclophosphamide; DTIC = dacarbazine; AC = doxorubicin and cyclophosphamide; EBRT = external beam radiation therapy; brachy = brachytherapy; IORT = intraoperative radiation therapy